Connecting via Winsock to STN

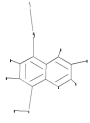
Welcome to STN International! Enter x:x

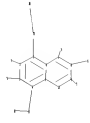
* * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:20:56 ON 25 FEB 2010

=>
=> file reg

=>
Uploading C:\Program Files\Stnexp\Queries\10534357.str





chain nodes :
11 12 13 14 15 16 17 18 20
ring nodes :

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1  2  3  4  5  6  7  8  9  10
chain bonds :
1-13  2-14  3-18  6-11  7-15  8-16  9-17  11-12  18-20
ring bonds :
1-2  1-6  2-3  3-4  4-5  4-7  5-6  5-10  7-8  8-9  9-10
exact/norm bonds :
6-11  18-20
exact bonds :
1-13  2-14  3-18  7-15  8-16  9-17  11-12
normalized bonds :
1-2  1-6  2-3  3-4  4-5  4-7  5-6  5-10  7-8  8-9  9-10


G1:C,S,N,Hy

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS  18:CLASS
20:CLASS



L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1                STR
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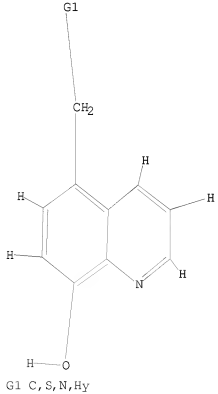


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G1 C,S,N,Hy
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Structure attributes must be viewed using STN Express query preparation.

=> s l1 sam
SAMPLE SEARCH INITIATED 14:21:36 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 1697 TO ITERATE

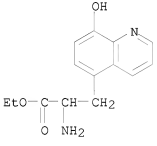
100.0% PROCESSED 1697 ITERATIONS 39 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 31469 TO 36411
PROJECTED ANSWERS: 406 TO 1154

L2 39 SEA SSS SAM L1

=> d scan

L2 39 ANSWERS REGISTRY COPYRIGHT 2010 ACS on STN
IN 5-Quinolinepropanoic acid, α-amino-8-hydroxy-, ethyl ester
MF C14 H16 N2 O3



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):end

=> s l1 full
FULL SEARCH INITIATED 14:21:46 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 33580 TO ITERATE

100.0% PROCESSED 33580 ITERATIONS 578 ANSWERS
SEARCH TIME: 00.00.01

L3 578 SEA SSS FUL L1

=> file ca

=> s l3
L4 258 L3

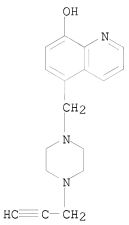
```
=> s iron chelat?
      1141221 IRON
       149890 CHELAT?
L5       6630 IRON CHELAT?
                (IRON(W)CHELAT?)

=> s l5 and l4
L6         20 L5 AND L4

=> d ibib abs fhitstr hitrn 1-20

L6   ANSWER 1 OF 20  CA  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:        152:67431  CA
TITLE:                   Neuroprotective and neuritogenic activities of novel
                         multimodal iron-chelating drugs in
                         motor-neuron-like NSC-34 cells and transgenic mouse
                         model of amyotrophic lateral sclerosis
AUTHOR(S):               Kupershmidt, Lana; Weinreb, Orly; Amit, Tamar; Mandel,
                         Silvia; Carri, Maria Teresa; Youdim, Moussa B. H.
CORPORATE SOURCE:        Eve Topf and USA National Parkinson Foundation Centers
                         of Excellence for Neurodegenerative Diseases Research,
                         Rappaport Family Research Institute, Faculty of
                         Medicine, Technion, Haifa, Israel
SOURCE:                  FASEB Journal (2009), 23(11), 3766-3779,
                         10.1096/fj.09-130047
                         CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER:               Federation of American Societies for Experimental
                         Biology
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Novel therapeutic approaches for the treatment of neurodegenerative
     disorders comprise drug candidates designed specifically to act on
     multiple central nervous system targets.  We have recently synthesized
     multifunctional, nontoxic, brain-permeable iron-
     chelating drugs, M30 and HLA20, possessing the N-propargylamine
     neuroprotective moiety of rasagiline (Azilect) and the iron-
     chelating moiety of VK28.  The present study demonstrates that M30
     and HLA20 possess a wide range of pharmacol. activities in mouse NSC-34
     motor neuron cells, including neuroprotective effects against hydrogen
     peroxide- and 3-morpholinosydnonimine-induced neurotoxicity, induction of
     differentiation, and up-regulation of hypoxia-inducible factor
     (HIF)-1α and HIF-target genes (enolase1 and vascular endothelial
     growth factor).  Both compds. induced NSC-34 neuritogenesis, accompanied
     by a marked increase in the expression of brain-derived neurotrophic
     factor and growth-associated protein-43, which was inhibited by PD98059 and
     GF109203X, indicating the involvement of mitogen-activated protein kinase
     and protein kinase C pathways.  A major finding was the ability of M30 to
     significantly extend the survival of G93A-SOD1 amyotrophic lateral
     sclerosis mice and delay the onset of the disease.  These properties of
     the novel multimodal iron-chelating drugs possessing
     neuroprotective/neuritogenic activities may offer future therapeutic
     possibilities for motor neurodegenerative diseases.
IT   686722-53-2
     RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU
     (Therapeutic use); BIOL (Biological study); USES (Uses)
        (neuroprotective and neuritogenic activities of novel multimodal
        iron-chelating drugs in motor-neuron-like NSC-34
```

cells and transgenic mouse model of amyotrophic lateral sclerosis)
RN 686722-53-2 CA
CN 8-Quinolinol, 5-[[4-(2-propyn-1-yl)-1-piperazinyl]methyl]- (CA INDEX NAME)



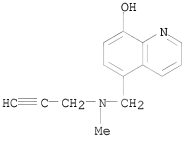
IT 686722-53-2
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotective and neuritogenic activities of novel multimodal iron-chelating drugs in motor-neuron-like NSC-34 cells and transgenic mouse model of amyotrophic lateral sclerosis)
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 152:51055 CA
TITLE: Multifunctional neuroprotective derivatives of rasagiline as anti-Alzheimer's disease drugs
AUTHOR(S): Weinreb, Orly; Mandel, Silvia; Bar-Am, Orit; Yogev-Falach, Merav; Avramovich-Tirosh, Yael; Amit, Tamar; Youdim, Moussa B. H.
CORPORATE SOURCE: Eve Topf and USA National Parkinson Foundation Centers of Excellence for Neurodegenerative Diseases Research and Department of Pharmacology, Rappaport Family Research Institute, Technion-Faculty of Medicine, Haifa, 31096, Israel
SOURCE: Neurotherapeutics (2009), 6(1), 163-174
CODEN: NEURNV; ISSN: 1933-7213
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The recent therapeutic approach in which drug candidates are designed to possess diverse pharmacol. properties and act on multiple targets has stimulated the development of the multimodal drugs, ladostigil (TV3326) [(N-propargyl-(3R) aminoindan-5yl)-Et Me carbamate] and the newly designed multifunctional antioxidant iron chelator, M-30 (5-[N-methyl-N-propargylaminomethyl]-8-hydroxyquinoline). Ladostigil combines, in a single mol., the neuroprotective/neurorestorative effects

of the novel anti-Parkinsonian drug and selective monoamine oxidase (MAO)-B inhibitor, rasagiline (Azilect, Teva Pharmaceutical Co.) with the cholinesterase (ChE) inhibitory activity of rivastigmine. A second derivative of rasagiline, M-30 was developed by amalgamating the propargyl moiety of rasagiline into the skeleton of our novel brain permeable neuroprotective iron chelator, VK-28. Preclin. expts. showed that both compds. have anti-Alzheimer's disease activities and thus, the clin. development is oriented toward treatment of this type of dementia. This review discusses the multimodal effects of two rasagiline-containing hybrid mols., namely ladostigil and M-30, concerning their neuroprotective mol. mechanisms in vivo and in vitro, including regulation of amyloid precursor protein processing, activation of protein kinase C, and mitogen-activated protein kinase signaling pathways, inhibition of cell death markers and upregulation of neurotrophic factors. Altogether, these scientific findings make these multifunctional compds. potentially valuable drugs for the treatment of Alzheimer's disease.

IT 766454-72-2
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M-30 and ladostigil showed neuroprotection by regulating amyloid precursor protein processing, activating PKC and MAPK signaling, inhibiting cell death markers and upregulating neurotrophic factors in patient with Alzheimer's disease)

RN 766454-72-2 CA
CN 8-Quinolinol, 5-[(methyl-2-propyn-1-ylamino)methyl]- (CA INDEX NAME)

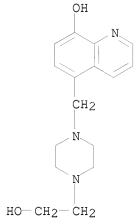


IT 766454-72-2
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M-30 and ladostigil showed neuroprotection by regulating amyloid precursor protein processing, activating PKC and MAPK signaling, inhibiting cell death markers and upregulating neurotrophic factors in patient with Alzheimer's disease)

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 136 THERE ARE 136 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 148:160056 CA
TITLE: Prevention and restoration of lactacystin-induced nigrostriatal dopamine neuron degeneration by novel brain-permeable iron chelators
AUTHOR(S): Zhu, Wen; Xie, Wenjie; Pan, Tianhong; Xu, Pingyi;

Fridkin, Mati; Zheng, Hailin; Jankovic, Joseph; Youdim, Moussa B. H.; Le, Weidong
CORPORATE SOURCE: Department of Neurology, Baylor College of Medicine, Houston, TX, USA
SOURCE: FASEB Journal (2007), 21(14), 3835-3844, 10.1096/fj.07-8386com
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Dysfunction of the ubiquitin-proteasome system (UPS) and accumulation of iron in substantia nigra (SN) are implicated in the pathogenesis of Parkinson's disease (PD). UPS dysfunction and iron misregulation may reinforce each other's contribution to the degeneration of dopamine (DA) neurons. In the present study, we use a new brain-permeable iron chelator, VK-28 [5-(4-(2-hydroxyethyl) piperazin-1-yl (methyl)-8-hydroxyquinoline], and its derivative M30 [5-(N-methyl-N-propargyaminomethyl)-8-hydroxyquinoline] in vivo to test their neuroprotective and neurorestorative properties against proteasome inhibitor (lactacystin) -induced nigrostriatal degeneration. Bilateral microinjections of lactacystin (1.25 μg/side) into the mouse medial forebrain bundle were performed. Administration of VK-28 (5 mg/kg, once a day) or M30 (5 mg/kg, once a day) was applied i.p. 7 days before or after the lactacystin microinjection until the mice were sacrificed 28 days after microinjection. We found that VK-28 and M30 both significantly improved behavioral performances and attenuated lactacystin-induced DA neuron loss, proteasomal inhibition, iron accumulation, and microglial activation in SN. In addition, M30 restored the Bcl-2 level, which was suppressed after lactacystin injection. These findings suggest that brain-permeable iron chelators can improve DA neuron survival under UPS impairment. Furthermore, M30, a derivative of VK-28 and neuroprotective agent rasagiline, may serve as a better neuroprotective therapy for PD.
IT 312611-92-0, VK-28
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention and restoration of lactacystin-induced nigrostriatal dopamine neuron degeneration by novel brain-permeable iron chelators)
RN 312611-92-0 CA
CN 8-Quinolinol, 5-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]- (CA INDEX NAME)



IT 312611-92-0, VK-28 766454-72-2
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention and restoration of lactacystin-induced nigrostriatal dopamine neuron degeneration by novel brain-permeable iron chelators)

OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 20 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 148:93017 CA

TITLE: Neurorescue activity, APP regulation and amyloid-β peptide reduction by novel multi-functional brain permeable iron-chelating- antioxidants, M-30 and green tea polyphenol, EGCG

AUTHOR(S): Avramovich-Tirosh, Yael; Reznichenko, Lydia; Amit, Tamar; Zheng, Hailin; Fridkin, Mati; Weinreb, Orly; Mandel, Silvia; Youdim, Moussa B. H.

CORPORATE SOURCE: Technion- Rappaport Family Faculty of Medicine and Department of Pharmacology, Eve Topf and USA NPF Centers of Excellence, Haifa, Israel

SOURCE: Current Alzheimer Research (2007), 4(4), 403-411
CODEN: CARUBY; ISSN: 1567-2050

PUBLISHER: Bentham Science Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

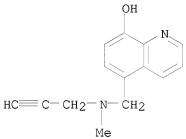
AB Accumulation of iron at sites where neurons degenerate in Parkinson's disease (PD) and Alzheimer's disease (AD) is thought to have a major role in oxidative stress induced process of neurodegeneration. The novel non-toxic lipophilic brain-permeable iron chelators, VK-28 (5-[4-(2-hydroxyethyl) piperazine-1-ylmethyl]-quinoline-8-ol) and its multi-functional derivative, M-30 (5-[N-methyl-N-propargylaminomethyl]-8-hydroxyquinoline), as well as the main polyphenol constituent of green tea (-)-epigallocatechin-3-gallate (EGCG), which possesses iron metal chelating, radical scavenging and neuroprotective properties, offer potential therapeutic benefits for these diseases. M-30 and EGCG

decreased apoptosis of human SH-SY5Y neuroblastoma cells in a neurorescue, serum deprivation model, via multiple protection mechanisms including: reduction of the pro-apoptotic proteins, Bad and Bax, reduction of apoptosis-associated Ser139 phosphorylated H2A.X and inhibition of the cleavage and activation of caspase-3. M-30 and EGCG also promoted morphol. changes, resulting in axonal growth-associated protein-43 (GAP-43) implicating neuronal differentiation. Both compds. significantly reduced the levels of cellular holo-amyloid precursor protein (APP) in SH-SY5Y cells. The ability of these novel iron chelators and EGCG to regulate APP are in line with the presence of an iron-responsive element (IRE) in the 5'-untranslated region (5'UTR) of APP. Also, EGCG reduced the levels of toxic amyloid-beta peptides in CHO cells over-expressing the APP "Swedish" mutation. The diverse mol. mechanisms and cell signaling pathways participating in the neuroprotective/neurorescue and APP regulation/processing actions of M-30 and EGCG, make these multifunctional compds. potential neuroprotective drugs for the treatment of neurodegenerative diseases, such as PD, AD, Huntington's disease and amyotrophic lateral sclerosis.

IT 766454-72-2P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(neurorescue activity, APP regulation and amyloid-β peptide reduction by novel multi-functional brain permeable iron-chelating- antioxidants, M-30 and green tea polyphenol, EGCG)

RN 766454-72-2 CA

CN 8-Quinolinol, 5-[(methyl-2-propyn-1-ylamino)methyl]- (CA INDEX NAME)



IT 766454-72-2P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(neurorescue activity, APP regulation and amyloid-β peptide reduction by novel multi-functional brain permeable iron-chelating- antioxidants, M-30 and green tea polyphenol, EGCG)

IT 312611-92-0, VK-28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neurorescue activity, APP regulation and amyloid-β peptide reduction by novel multi-functional brain permeable iron-chelating- antioxidants, M-30 and green tea polyphenol, EGCG)

OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 147:44903 CA
TITLE: Implications of co-morbidity for etiology and treatment of neurodegenerative diseases with multifunctional neuroprotective-neurorescue drugs; ladostigil
AUTHOR(S): Youdim, Moussa B. H.; Amit, Tamar; Bar-Am, Orit; Weinreb, Orly; Yogev-Falach, Mara
CORPORATE SOURCE: Eve Topf and NPF Centers for Neurodegenerative Diseases, Department of Pharmacology, Technion-Rappaport Family Faculty of Medicine, Haifa, Israel
SOURCE: Neurotoxicity Research (2006), 10(3,4), 181-192
CODEN: NURRFI; ISSN: 1029-8428
PUBLISHER: F. P. Graham Publishing Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

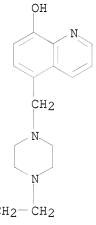
AB A review. The recent therapeutic approach in which drug candidates are designed to possess diverse pharmacol. properties and act on multiple targets has stimulated the development of several multifunction drugs. These include ladostigil (TV3326) [(N-propargyl-(3R) aminoindan-5yl)-Et Me carbamate], which combines the pharmacophore-neuroprotective effects of rasagiline, a selective monoamine oxidase (MAO)-B inhibitor, with the cholinesterase (ChE) inhibitory activity of rivastigmine or iron chelating moiety such as M30. In the case of M30 the pharmacophore of brain permeable iron chelator VK-28 plus the MAO inhibitor-neuroprotective propargylamine moiety of rasagiline are combined in a single mol. as a potential treatment for Alzheimer's disease, Lewy body disease, and Parkinson's disease with dementia. Here, we discuss the activities of ladostigil in terms of its cholinesterase cognitive enhancing potential, antiParkinson, antidepressant, neuroprotection and APP (amyloid precursor protein) processing potential. One major attribute of ladostigil is its neuroprotective activity in neuronal cell cultures and in vivo. Employing an apoptotic model of neuroblastoma SK-N-SH cells, the mol. mechanism of its neuroprotective activity has been determined The current studies show that ladostigil significantly decreased apoptosis via inhibition of the cleavage and prevention of caspase-3 activation through a mechanism related to regulation of the Bcl-2 family proteins, resulting in reduced levels of Bad and Bax and induced levels of Bcl-2. In addition, ladostigil elevated the levels of pPKC(pan). We have also followed the regulation of APP processing and found that ladostigil markedly decreased apoptotic-induced levels of holo-APP, as well as stimulated the release of the non-amyloidogenic soluble APP (sAPPα) into the conditioned medium via a established protein kinsae c-MAPkinase dependent pathway. Similar to ladostigil, its S-isomer, TV3279, which is a ChE inhibitor lacking MAO inhibitory activity, exerted similar neuroprotective properties and APP processing, suggesting that the mode of action is independent of MAO inhibition. These effects were shown to reside in the propargylamine moiety. These findings indicate that the dual actions of the anti-apoptotic-neuroprotective activity and the ability to modulate APP processing, could make ladostigil a potentially valuable drug for the treatment of Alzheimer's disease.

IT 312611-92-0, VK-28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(multifunctional neuroprotective-neurorescue effects of ladostigil on implications of co-morbidity for etiol. and treatment of neurodegenerative diseases)

RN 312611-92-0 CA

CN 8-Quinolinol, 5-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]- (CA INDEX NAME)



IT 312611-92-0, VK-28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(multifunctional neuroprotective-neurorescue effects of ladostigil on implications of co-morbidity for etiol. and treatment of neurodegenerative diseases)

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 20 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 146:395039 CA

TITLE: Therapeutic targets and potential of the novel brain-permeable multifunctional iron chelator-monoamine oxidase inhibitor drug, M-30, for the treatment of Alzheimer's disease

AUTHOR(S): Avramovich-Tirosh, Yael; Amit, Tamar; Bar-Am, Orit; Zheng, Hailin; Fridkin, Mati; Youdim, Moussa B. H.

CORPORATE SOURCE: Eve Topf Centers of Excellence, Technion-Rappaport Family Faculty of Medicine and Department of Pharmacology, Haifa, Israel

SOURCE: Journal of Neurochemistry (2007), 100(2), 490-502
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

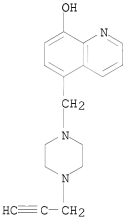
AB Novel therapeutic approaches for the treatment of neurodegenerative disorders comprise drug candidates designed specifically to act on multiple CNS targets. We have synthesized a multifunctional non-toxic, brain permeable iron chelator drug, M-30, possessing propargyl monoamine oxidase (MAO) inhibitory neuroprotective and iron-chelating moieties, from our prototype iron

chelator VK-28. In the present study M-30 was shown to possess a wide range of pharmacol. activities, including pro-survival neurorescue effects, induction of neuronal differentiation and regulation of amyloid precursor protein (APP) and β-amyloid (Aβ) levels. M-30 was found to decrease apoptosis of SH-SY5Y neuroblastoma cells in a neurorescue, serum deprivation model, via reduction of the pro-apoptotic proteins Bad and Bax, and inhibition of the apoptosis-associated phosphorylated H2A.X protein (Ser 139) and caspase 3 activation. In addition, M-30 induced the out-growth of neurites, triggered cell cycle arrest in G0/G1 phase and enhanced the expression of growth associated protein-43. Furthermore, M-30 markedly reduced the levels of cellular APP and β-C-terminal fragment (β-CTF) and the levels of the amyloidogenic Aβ peptide in the medium of SH-SY5Y cells and Chinese hamster ovary cells stably transfected with the APP 'Swedish' mutation. Levels of the non-amyloidogenic soluble APPα and α-CTF in the medium and cell lysate resp. were coordinately increased. These properties, together with its brain selective MAO inhibitory and propargylamine-dependent neuroprotective effects, suggest that M-30 might serve as an ideal drug for neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases, in which oxidative stress and iron dysregulation have been implicated.

IT 686722-53-2, HLA 20
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HLA 20; iron chelator-monoamine oxidase inhibitor M-30 for treatment of Alzheimer's disease)

RN 686722-53-2 CA

CN 8-Quinolinol, 5-[[4-(2-propyn-1-yl)-1-piperazinyl]methyl]- (CA INDEX NAME)



IT 686722-53-2, HLA 20
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HLA 20; iron chelator-monoamine oxidase inhibitor M-30 for treatment of Alzheimer's disease)

IT 766454-72-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M 30; iron chelator-monoamine oxidase inhibitor M-30 for treatment of Alzheimer's disease)

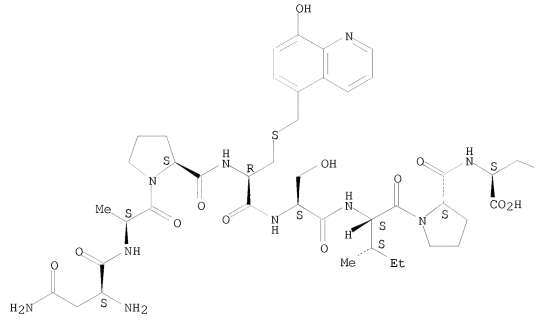
IT 312611-92-0, VK-28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(iron chelator-monoamine oxidase inhibitor M-30 for treatment of Alzheimer's disease)
OS.CITING REF COUNT: 18 THERE ARE 18 CAPLUS RECORDS THAT CITE THIS RECORD (18 CITINGS)
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 146:395013 CA
TITLE: Novel neuroprotective neurotrophic NAP analogs targeting metal toxicity and oxidative stress: potential candidates for the control of neurodegenerative diseases
AUTHOR(S): Zheng, H.; Blat, D.; Fridkin, M.
CORPORATE SOURCE: Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel
SOURCE: Journal of Neural Transmission, Supplement (2006), 71(Oxidative Stress and Neuroprotection), 163-172
CODEN: JNTSD4; ISSN: 0303-6995
PUBLISHER: Springer Wien
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A large body of data indicates that a cascade of events contributes to the neurodegeneration in Alzheimer's disease (AD) and Parkinson's disease (PD). Metal (Fe, Cu, Zn) dyshomeostasis and oxidative stress are believed to play a pivotal role in the pathogenesis of these diseases. Accordingly, multifunctional compds. combining metal chelating and antioxidative activity hold a great promise as potential drugs for treating AD and PD. In this study, two novel NAPVSIPQ (NAP) analogs (M98 and M99) with potential antioxidant-metal chelating ability were designed and investigated, aiming to improve the poor metal chelating and antioxidative activity of NAP. The authors' studies showed that both M98 and M99 formed stable metal (Fe, Cu, Zn) complexes in water and demonstrated good metal (Fe, Cu, Zn) chelating properties as opposed to the poor metal (Fe, Cu, Zn) chelating properties of their parent peptide NAP. M98 and M99 exhibited significant inhibition of iron-induced lipid peroxidn. in rat brain homogenates at concns. of ≥30 μM, while NAP failed to show any inhibition even at 100 μM. In human neuroblastoma cell (SH-SY5Y) culture, M98 and M99 at 1 μM completely protected against 6-hydroxydopamine (6OHDA) toxicity with potency similar to NAP and desferal (DFO), a strong iron chelator and a highly potent radical scavenger. In PC12 cell culture, M98 at the range of 0.001-1 μM displayed potent protection against 6-OHDA toxicity, comparable to NAP and DFO. These results suggest that M98 and M99 deserve further investigation as potential drug candidates for neuroprotection.
IT 934013-22-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NAPVSIPQ analog M99 inhibited iron-induced lipid peroxidn. in rat brain and protected against 6-hydroxydopamine toxicity in PC12 cells and human neuroblastoma cells)
RN 934013-22-6 CA
CN L-Glutamine, L-asparaginyl-L-alanyl-L-prolyl-S-[(8-hydroxy-5-quinolinyl)methyl]-L-cysteinyl-L-seryl-L-isoleucyl-L-prolyl- (CA INDEX

NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

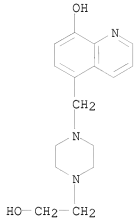
IT 934013-22-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NAPVSIPQ analog M99 inhibited iron-induced lipid peroxidn. in rat brain and protected against 6-hydroxydopamine toxicity in PC12 cells and human neuroblastoma cells)
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 146:220867 CA
TITLE: Metal specificity of an iron-responsive element in Alzheimer's APP mRNA 5' untranslated region, tolerance of SH-SY5Y and H4 neural cells to desferrioxamine, clioquinol, VK-28, and a piperazine chelator
AUTHOR(S): Bandyopadhyay, S.; Huang, X.; Cho, H.; Greig, N. H.; Youdim, M. B.; Rogers, J. T.
CORPORATE SOURCE: Neurochemistry Laboratory, Department of Psychiatry, Genetics and Aging Research Unit, Massachusetts General Hospital, USA
SOURCE: Journal of Neural Transmission, Supplement (2006), 71(Oxidative Stress and Neuroprotection), 237-247
CODEN: JNTSD4; ISSN: 0303-6995
PUBLISHER: Springer Wien
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Iron closely regulates the expression of the Alzheimer's Amyloid Precursor Protein (APP) gene at the level of message translation by a pathway similar to iron control of the translation of the ferritin L- and H mRNAs by Iron-responsive Elements in their 5' untranslated regions (5'UTRs). Using transfection based assays in SH-SY5Y neuroblastoma cells we tested the relative efficiency by which iron, copper and zinc up-regulate IRE activity in the APP 5'UTR. Desferrioxamine (high affinity Fe3+ chelator), (ii) clioquinol (low affinity Fe/Cu/Zn chelator), (iii) piperazine-1 (oral Fe chelator), (iv) VK-28 (oral Fe chelator), were tested for their relative modulation of APP 5'UTR directed translation of a luciferase reporter gene. Iron chelation based therapeutic strategies for slowing the progression of Alzheimer's disease (and other neurol. disorders that manifest iron imbalance) are discussed with regard to the relative neural toxic action of each chelator in SH-SY5Y cells and in H4 glioblastoma cells.

IT 312611-92-0, VK-28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(VK-28 effectively inhibited Alzheimer's amyloid precursor protein 5'untranslated region conferred luciferase gene expression compared to desferrioxamine, clioquinol and piperazine-1 in neuroblastoma and glioblastoma cells)
RN 312611-92-0 CA
CN 8-Quinolinol, 5-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]- (CA INDEX NAME)



IT 312611-92-0, VK-28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(VK-28 effectively inhibited Alzheimer's amyloid precursor protein 5'untranslated region conferred luciferase gene expression compared to desferrioxamine, clioquinol and piperazine-1 in neuroblastoma and glioblastoma cells)

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 9 OF 20 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 146:134336 CA

TITLE: M30, a novel multifunctional neuroprotective drug with potent iron chelating and brain selective monoamine oxidase-ab inhibitory activity for Parkinson's disease

AUTHOR(S): Gal, S.; Fridkin, M.; Amit, T.; Zheng, H.; Youdim, M. B. H.

CORPORATE SOURCE: Technion-Faculty of Medicine, Eve Topf and US National Parkinson Foundation Centers of Excellence for Neurodegenerative Diseases, Haifa, Israel

SOURCE: Journal of Neural Transmission, Supplement (2006), 70(Parkinson's Disease and Related Disorders), 447-456
CODEN: JNTSD4; ISSN: 0303-6995

PUBLISHER: Springer Wien

DOCUMENT TYPE: Journal; General Review

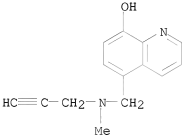
LANGUAGE: English

AB A review. Iron and monoamine oxidase activity are increased in brain of Parkinson's disease (PD). They are associated with autoxidn. and oxidative deamination of dopamine by MAO resulting in the generation of reactive oxygen species and the onset of oxidative stress to induce neurodegeneration. Iron chelators (desferal, Vk-28 and clioquinol) but not copper chelators have been shown to be neuroprotective in the 6-hydroxydopamine and MPTP models of Parkinson's disease (PD), as are monoamine oxidase B inhibitors such as selegiline and rasagiline. These findings prompted the development of multifunctional anti PD drugs possessing iron chelating pharmacophore

of VK-28 and the propargylamine MAO inhibitory activity of rasagiline. M30 is a potent iron chelator, radical scavenger and brain selective irreversible MAO-A and B inhibitor, with little inhibition of peripheral MAO. It has neuroprotective activity in in vitro and in vivo models of PD and unlike selective MAO-B inhibitors it increases brain dopamine, serotonin and noradrenaline. These findings indicate beside its anti PD action, it may also possess antidepressant activity, similar to selective MAO-A and nonselective MAO inhibitors. These properties make it an ideal anti PD drug for which it is being developed.

IT 766454-72-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activated; M30 revealed both neuroprotectant and brain selective monoamine oxidase A and B inhibitory activity in vitro and in exptl. animal models hence could be ideal drug for treatment of Parkinson's disease)

RN 766454-72-2 CA
CN 8-Quinolinol, 5-[(methyl-2-propyn-1-ylamino)methyl]- (CA INDEX NAME)



IT 766454-72-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activated; M30 revealed both neuroprotectant and brain selective monoamine oxidase A and B inhibitory activity in vitro and in exptl. animal models hence could be ideal drug for treatment of Parkinson's disease)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 144:480 CA
TITLE: Novel potential neuroprotective agents with both iron chelating and amino acid-based derivatives targeting central nervous system neurons
AUTHOR(S): Zheng, Hailin; Youdim, Moussa B. H.; Weiner, Lev M.; Fridkin, Mati
CORPORATE SOURCE: Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Biochemical Pharmacology (2005), 70(11), 1642-1652 CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

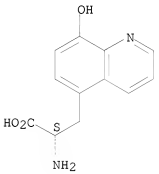
AB Antioxidants and iron chelating mols. are known as neuroprotective agents in animal models of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). In this study, we designed and synthesized a novel bifunctional mol. (M10) with radical scavenging and iron chelating ability on an amino acid carrier likely to be a substrate for system L, thus targeting the compound to the central nervous system (CNS). M10 had a moderate iron affinity in HEPES buffer (pH 7.4) with log K 3 = 12.25±0.55 but exhibited highly inhibitory action against iron-induced lipid peroxidn., with an IC50 value (12 μM) comparable to that of desferal (DFO). EPR studies indicated that M10 was a highly potent ·OH scavenger with an IC50 of about 0.3 molar ratio of M10 to H2O2. In PC12 cell culture, M10 was at least as potent as the anti-Parkinson drug rasagiline in protecting against cell death induced by serum-deprivation and by 6-hydroxydopamine (6-OHDA). These results suggest that M10 deserves further investigation as a potential agent for the treatment of neurodegenerative disorders such as AD and PD.

IT 72903-50-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(potential neuroprotective agents with both iron chelating and amino acid-based derivs. targeting central nervous system neurons)

RN 72903-50-5 CA

CN 5-Quinolinepropanoic acid, α-amino-8-hydroxy-, (αS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



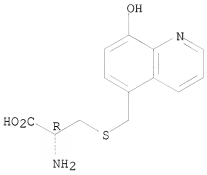
IT 72903-50-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(potential neuroprotective agents with both iron chelating and amino acid-based derivs. targeting central nervous system neurons)

IT 23279-45-0P 686722-47-4P 686722-48-5P 686722-49-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(potential neuroprotective agents with both iron chelating and amino acid-based derivs. targeting central

nervous system neurons)
IT 686722-50-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(potential neuroprotective agents with both iron chelating and amino acid-based derivs. targeting central nervous system neurons)
OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 143:478192 CA
TITLE: Synthesis and evaluation of peptidic metal chelators for neuroprotection in neurodegenerative diseases
AUTHOR(S): Zheng, H.; Youdim, M. B. H.; Weiner, L. M.; Fridkin, M.
CORPORATE SOURCE: Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Journal of Peptide Research (2005), 66(4), 190-203
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:478192
AB A series of novel derivs. of neuropeptides with a metal-chelating moiety was synthesized and examined for various properties related to iron (Fe) chelation and neuroprotective action. All derivs. chelated Fe to form stable Fe complexes in water. Some strongly inhibited Fe-induced lipid peroxidn. with an IC50 value of about 12 μM. In PC12 cell culture, several compds. at concns. as low as 1 μM, attenuated serum-free stimulated cell death and improved cell survival by 20-35%. At this concentration, these analogs also protected against 6-hydroxydopamine (6-OHDA)-induced cell death, increasing cell viability by 20-30%. ESR studies indicated that besides being good Fe chelators, these analogs act as radical scavengers to directly scavenge hydroxyl radicals. Together, the data indicate that some of the analogs could be further developed as possible neuroprotective agents for treatment of neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's diseases, Friedreich's atxia, amyotrophic, and lateral sclerosis where Fe misregulation has been reported.
IT 686722-58-7P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of peptidic metal chelators for neuroprotection in neurodegenerative diseases)
RN 686722-58-7 CA
CN L-Cysteine, S-[(8-hydroxy-5-quinolinyl)methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 686722-58-7P 686722-77-0P 686722-82-7P
686722-84-9P 686722-86-1P 686722-90-7P
686722-91-8P 686722-94-1P 686722-95-2P
686722-96-3P 686722-97-4P 869743-30-6P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of peptidic metal chelators for neuroprotection in neurodegenerative diseases)

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 20 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 143:416029 CA

TITLE: Novel multifunctional neuroprotective iron chelator-monoamine oxidase inhibitor drugs for neurodegenerative diseases. In vivo selective brain monoamine oxidase inhibition and prevention of MPTP-induced striatal dopamine depletion

AUTHOR(S): Gal, Shunit; Zheng, Hailin; Fridkin, Mati; Youdim, Moussa B. H.

CORPORATE SOURCE: Technion-Rappaport Family Faculty of Medicine and Department of Pharmacology, Eve Topf and US National Parkinson Foundation Centers of Excellence for Neurodegenerative Diseases, Haifa, Israel

SOURCE: Journal of Neurochemistry (2005), 95(1), 79-88
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

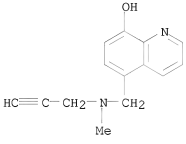
AB Several multifunctional iron chelators have been synthesized from hydroxyquinoline pharmacophore of the iron chelator, VK-28, possessing the monoamine oxidase (MAO) and neuroprotective N-propargylamine moiety. They have iron chelating potency similar to desferal. M30 is a potent irreversible rat brain mitochondrial MAO-A and -B inhibitor in vitro (IC50, MAO-A, 0.037±0.02; MAO-B, 0.057±0.01). Acute (1-5 mg/kg) and chronic [5-10 mg/kg i.p., or orally (p.o.) once daily for 14 days] in vivo studies have shown M30 to be a potent brain selective (striatum, hippocampus and cerebellum) MAO-A and -B inhibitor. It has little effects

on the enzyme activities of the liver and small intestine. Its N-des-methylated derivative, M30A is significantly less active. Acute and chronic treatment with M30 results in increased levels of dopamine (DA), serotonin(5-HT), noradrenaline (NA) and decreases in DOPAC (dihydroxyphenylacetic acid), HVA (homovanillic acid) and 5-HIAA (5-hydroxyindole acetic acid) as determined in striatum and hypothalamus. In the mouse MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of Parkinson's disease (PD) it attenuates the DA depleting action of the neurotoxin and increases striatal levels of DA, 5-HT and NA, while decreasing their metabolites. As DA is equally well metabolized by MAO-A and -B, it is expected that M30 would have a greater DA neurotransmission potentiation in PD than selective MAO-B inhibitors, for which it is being developed, as MAO-B inhibitors do not alter brain dopamine.

IT 766454-72-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of monoamine oxidase and dopamine depletion by neuroprotective iron chelator-monoamine oxidase inhibitor drugs)

RN 766454-72-2 CA

CN 8-Quinolinol, 5-[(methyl-2-propyn-1-ylamino)methyl]- (CA INDEX NAME)



IT 766454-72-2 848645-94-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of monoamine oxidase and dopamine depletion by neuroprotective iron chelator-monoamine oxidase inhibitor drugs)

OS.CITING REF COUNT: 43 THERE ARE 43 CAPLUS RECORDS THAT CITE THIS RECORD (43 CITINGS)

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 20 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 143:416028 CA

TITLE: Novel multifunctional neuroprotective iron chelator-monoamine oxidase inhibitor drugs for neurodegenerative diseases: in vitro studies on antioxidant activity, prevention of lipid peroxide formation and monoamine oxidase inhibition

AUTHOR(S): Zheng, Hailin; Gal, Shunit; Weiner, Lev M.; Bar-Am, Orit; Warshawsky, Abraham; Fridkin, Mati; Youdim, Moussa B. H.

CORPORATE SOURCE: Department of Organic Chemistry and Neurobiology, The Weizmann Institute of Science, Rehovot, Israel

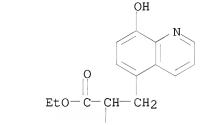
SOURCE: Journal of Neurochemistry (2005), 95(1), 68-78
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Iron-dependent oxidative stress, elevated levels of iron and of monoamine oxidase (MAO)-B activity, and depletion of antioxidants in the brain may be major pathogenic factors in Parkinson's disease, Alzheimer's disease and related neurodegenerative diseases. Accordingly, iron chelators, antioxidants and MAO-B inhibitors have shown efficacy in a variety of cellular and animal models of CNS injury. In searching for novel antioxidant iron chelators with potential MAO-B inhibitory activity, a series of new iron chelators has been designed, synthesized and investigated. In this study, the novel chelators were further examined for their activity as antioxidants, MAO-B inhibitors and neuroprotective agents in vitro. Three of the selected chelators (M30, HLA20 and M32) were the most effective in inhibiting iron-dependent lipid peroxidn. in rat brain homogenates with IC50 values (12-16 μM), which is comparable with that of desferal, a prototype iron chelator that is not has orally active. Their antioxidant activities were further confirmed using ESR spectroscopy. In PC12 cell culture, the three novel chelators at 0.1 μM were able to attenuate cell death induced by serum deprivation and by 6-hydroxydopamine. M30 possessing propargyl, the MAO inhibitory moiety of the anti-Parkinson drug rasagiline, displayed greater neuroprotective potency than that of rasagiline. In addition, in vitro, M30 was a highly potent non-selective MAO-A and MAO-B inhibitor (IC50 < 0.1 μM). However, HLA20 was more selective for MAO-B but had poor MAO inhibition, with an IC50 value of 64.2 μM. The data suggest that M30 and HLA20 might serve as leads in developing drugs with multifunctional activities for the treatment of various neurodegenerative disorders.

IT 686723-15-9, M 31
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M 31; antioxidant, iron-chelating, and MAO-inhibiting activity of multifunctional drugs for neurodegenerative diseases)

RN 686723-15-9 CA

CN 5-Quinolinepropanoic acid, 8-hydroxy-α-(2-propyn-1-ylamino)-, ethyl ester (CA INDEX NAME)



IT 686723-15-9, M 31
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M 31; antioxidant, iron-chelating, and

MAO-inhibiting activity of multifunctional drugs for neurodegenerative diseases)
IT 686723-14-8, M 32
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M 32; antioxidant, iron-chelating, and MAO-inhibiting activity of multifunctional drugs for neurodegenerative diseases)
IT 312611-92-0, VK28 686722-53-2, HLA 20
686722-58-7 686722-59-8 686722-62-3
686722-63-4 766454-72-2 848645-94-3, M 30A
868061-44-3, M 30B
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antioxidant, iron-chelating, and MAO-inhibiting activity of multifunctional drugs for neurodegenerative diseases)
OS.CITING REF COUNT: 40 THERE ARE 40 CAPLUS RECORDS THAT CITE THIS RECORD (40 CITINGS)
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

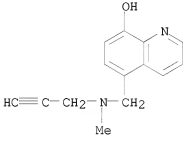
L6 ANSWER 14 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 142:328601 CA
TITLE: Bifunctional drug derivatives of MAO-B inhibitor rasagiline and iron chelator VK-28 as a more effective approach to treatment of brain ageing and ageing neurodegenerative diseases
AUTHOR(S): Youdim, Moussa B. H.; Fridkin, Mati; Zheng, Hailin
CORPORATE SOURCE: Eve Topf and US National Parkinson Foundation Centers of Excellence for Neurodegenerative Diseases Research and Department of Pharmacology, Technion Faculty of Medicine, Haifa, 31096, Israel
SOURCE: Mechanisms of Ageing and Development (2005), 126(2), 317-326
CODEN: MAGDA3; ISSN: 0047-6374
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Degeneration of nigrostriatal dopamine neurons and cholinergic cortical neurons are the main pathol. features of Parkinson's disease (PD) and for the cognitive deficit in dementia of the Alzheimer' type (AD) and in dementia with Lewy bodies (DLB), resp. Many PD and DLB subjects have dementia and depression resulting from possible degeneration of cholinergic and noradrenergic and serotonergic neurons. On the other hand, AD patients may also develop extrapyramidal features as well as depression. In both PD and AD there is, resp., accumulation of iron within the melanin containing dopamine neurons of pars compacta and with in the plaques and tangle. It has been suggested that iron accumulation may contribute to the oxidative stress induced apoptosis reported in both diseases. This may result from increased glia hydrogen peroxide producing monoamine oxidase (MAO) activity that can generate of reactive hydroxyl radical formed from interaction of iron and hydrogen peroxide. We have therefore prepared a series of novel bifunctional drugs from the neuroprotective-antiapoptotic antiparkinson monoamine oxidase B inhibitor, rasagiline, by introducing a carbamate cholinesterase (ChE) inhibitory moiety into it. Ladostigil ((TV-3326, N-propargyl-3R-aminoindan-5yl)-Et methylcarbamate), has both ChE and MAO-AB inhibitory activity, as

potential treatment of AD and DLB or PD subjects with dementia Being a brain selective MAO-AB inhibitor it has limited potentiation of the pressor response to oral tyramine and exhibits antidepressant activity similar to classical non-selective MAO inhibitor antidepressants by increasing brain serotonin and noradrenaline. Ladostigil inhibits brain acetyl and butyrylcholinesterase in rats and antagonizes scopolamine-induced inhibition of spatial learning. Ladostigil like MAO-B inhibitor it prevents MPTP Parkinsonism in mice model and retains the in vitro and in vivo neuroprotective activity of rasagiline. Ladostigil, rasagiline and other propargylamines have been demonstrated to have neuroprotective activity in several in vitro and in vivo models, which have been shown be associated with propargylamines moiety, since propargylamines itself possess these properties. The mechanism of neuroprotective activity has been attributed to the ability of propargylamines-inducing the antiapoptotic family proteins Bcl-2 and Bcl-xl, while decreasing Bad and Bax and preventing opening of mitochondrial permeability transition pore. Iron accumulates in brain regions associated with neurodegenerative diseases of PD, AD, amyotrophic lateral sclerosis and Huntington disease. It is thought to be involved in Fenton chemical oxidative stress observed in these diseases. The neuroprotective activity of propargylamines led us to develop several novel bifunctional iron chelator from our prototype brain permeable iron chelators, VK-28, possessing propargylamine moiety (HLA-20, M30 and M30A) to iron out iron from the brain. These compds. have been shown to have iron chelating and monoamine oxidase A and B selective brain inhibitory and neuroprotective-antiapoptotic actions.

IT 766454-72-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activated; bifunctional iron chelator from prototype brain permeable iron chelators VK-28, possessing propargylamine moiety M30 to iron out iron from brain have neuroprotective-antiapoptotic action)

RN 766454-72-2 CA

CN 8-Quinolinol, 5-[(methyl-2-propyn-1-ylamino)methyl]- (CA INDEX NAME)

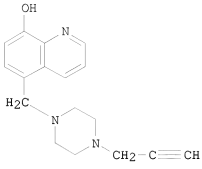


IT 766454-72-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activated; bifunctional iron chelator from prototype brain permeable iron chelators VK-28, possessing propargylamine moiety M30 to iron out iron from brain have neuroprotective-antiapoptotic action)

IT 686722-53-2, HLA 20

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bifunctional iron chelator from prototype brain permeable iron chelators VK-28, possessing propargylamine moiety HLA-20 to iron out iron from brain have neuroprotective-antiapoptotic action)
IT 312611-92-0, VK-28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bifunctional iron chelator from prototype brain permeable iron chelators VK-28, possessing propargylamine moiety HLA-20, M30, M30A to iron out iron from brain have neuroprotective-antiapoptotic action)
IT 848645-94-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bifunctional iron chelator from prototype brain permeable iron chelators VK-28, possessing propargylamine moiety M30A to iron out iron from brain have neuroprotective-antiapoptotic action)
OS.CITING REF COUNT: 43 THERE ARE 43 CAPLUS RECORDS THAT CITE THIS RECORD (44 CITINGS)
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 142:273353 CA
TITLE: Design, synthesis, and evaluation of novel bifunctional iron-chelators as potential agents for neuroprotection in Alzheimer's, Parkinson's, and other neurodegenerative diseases
AUTHOR(S): Zheng, Hailin; Weiner, Lev M.; Bar-Am, Orit; Epsztejn, Silvina; Cabantchik, Z. Ioav; Warshawsky, Abraham; Youdim, Moussa B. H.; Fridkin, Mati
CORPORATE SOURCE: Department of Organic Chemistry and Neurobiology, The Weizmann Institute of Science, Rehovot, 76100, Israel
SOURCE: Bioorganic & Medicinal Chemistry (2005), 13(3), 773-783
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:273353
GI



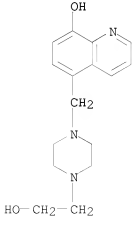
I

AB Several novel antioxidant-iron chelators bearing 8-hydroxyoxyquinoline moiety were synthesized, and various properties related to their iron chelation, and neuroprotective action were investigated. All the chelators exhibited strong iron(III) chelating and high antioxidant properties. Chelator I (HLA20), having good permeability into K562 cells and moderate selective MAO-B inhibitory activity (IC50 110 μM), displayed the highest protective effects against differentiated P19 cell death induced by 6-hydroxydopamine. EPR studies suggested that Chelator I also act as radical scavenger to directly scavenge hydroxyl radical.

IT 312611-92-0P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and evaluation of hydroxyoxyquinolines as iron-chelators with potential neuroprotective activity)

RN 312611-92-0 CA

CN 8-Quinolinol, 5-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]- (CA INDEX NAME)



IT 312611-92-0P 312611-93-1P 686722-53-2P
686723-15-9P 766454-72-2P 847232-07-9P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and evaluation of hydroxyoxyquinolines as iron-chelators with potential neuroprotective activity)
IT 686722-48-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and evaluation of hydroxyoxyquinolines as iron-chelators with potential neuroprotective activity)
IT 847232-06-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and evaluation of hydroxyoxyquinolines as iron-chelators with potential neuroprotective activity)
OS.CITING REF COUNT: 62 THERE ARE 62 CAPLUS RECORDS THAT CITE THIS RECORD (64 CITINGS)
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

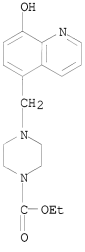
L6 ANSWER 16 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 142:169772 CA
TITLE: Novel bifunctional drugs targeting monoamine oxidase inhibition and iron chelation as an approach to neuroprotection in Parkinson's disease and other neurodegenerative diseases
AUTHOR(S): Youdim, M. B. H.; Fridkin, M.; Zheng, H.
CORPORATE SOURCE: Eve Topf and National Parkinson Foundation Centers of Excellence for Neurodegenerative Diseases Research, and Department of Pharmacology, Technion-Rapapport Faculty of Medicine, Haifa, Israel
SOURCE: Journal of Neural Transmission (2004), 111(10-11), 1455-1471
CODEN: JNTRF3; ISSN: 0300-9564
PUBLISHER: Springer Wien
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Iron has been shown to accumulates at site where neurons degenerate in neurodegenerative diseases of Parkinson's disease, Alzheimer's disease, Huntington disease, amyotrophic lateral sclerosis and Friedreich ataxia. Iron is thought to participate or initiate oxidative stress via generation of reactive oxygen species (ROS), such as hydroxyl radical. Iron chelators are neuroprotective and prevent 6-hydroxydoapmine and MPTP dopaminergic neurotoxicity in rats and mice. However, their action on monoamine oxidase (MAO) A and B have not been determined previously since MAO-B inhibitors have been shown to be neuroprotective in cellular and animal models of Parkinson's disease. The chelators 8-hydroxyquinoline, O-phenanthroline, 2,2'-dipyridyl, U74500A and U74600F showed a preference for inhibition of rat brain mitochondrial MAO-A over MAO-B. Their IC50 ranged from 10-3 M to 10-6 M, with 21-amino steroids (U74500A and U74006F) showing a greater selectivity and potency for MAO-A. Desferrioxamine (desferal), a prototype potent iron chelator, exhibited relatively poor MAO inhibitory. The inhibitions of MAO-A and B by 21-amino steroids (Lazaroids) were time dependent and irreversible. Those initiated by 8-hydroxyquinoline, 2,2'-dipyridyl and O-phenanthroline were fully reversible by enzyme dilution expts. Both Fe2+ and Fe3+ reverse

the MAO-A and B inhibition induced by the latter chelators, but not those initiated by 21-amino steroids. The data infer that either the inhibition of MAO by 21-amino steroids is either the resultant of their conversion to an irreversible covalently bound ligand or that the iron chelation moiety and MAO inhibitory activity in these compds. are not mutually shared. The results suggest that bifunctional brain penetrable drugs with iron chelating property and MAO inhibitory activity in could be the most feasible approach for neuroprotection in neurodegenerative diseases. Such drug would prevent participation of elevated iron in oxidative stress and formation of reactive hydroxyl radical, via its interaction with H2O2 (Fenton chemical), generated as a consequence MAO and other oxidative enzyme reactions to generative cytotoxic reactive hydroxyl radical. We have now developed several of these compds. with neuroprotective, MAO inhibitory and iron chelating properties from our prototype iron chelators, VK-28 possessing propargylamine moiety of our anti-parkinson drug, rasagiline.

IT 312611-93-1, HLA 16
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HLA16 propargylamine derivative of iron chelator VK-28 had higher inhibitory effect on monoamine oxidase-A and monoamine oxidase-B than VK-28)

RN 312611-93-1 CA

CN 1-Piperazinecarboxylic acid, 4-[(8-hydroxy-5-quinolinyl)methyl]-, ethyl ester (CA INDEX NAME)



IT 312611-93-1, HLA 16
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HLA16 propargylamine derivative of iron chelator VK-28 had higher inhibitory effect on monoamine oxidase-A and monoamine oxidase-B than VK-28)

IT 686722-53-2, HLA 20
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HLA20 propargylamine derivative of iron chelator VK-28 was highly selective for inhibition of monoamine oxidase-B than

monoamine oxidase-A in rat brain mitochondria)
IT 766454-72-2, M 30
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M30 propargylamine derivative of iron chelator VK-28 was highly potent in inhibiting monoamine oxidase-A and monoamine oxidase-B in rat brain mitochondria)
IT 686723-15-9, M 31
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M31 propargylamine derivative of iron chelator VK-28 was inactive for inhibition of monoamine oxidase-B than monoamine oxidase-A in rat brain mitochondria)
IT 686723-14-8, M 32
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(M32 propargylamine derivative of iron chelator VK-28 was inactive for inhibition of monoamine oxidase-B than monoamine oxidase-A in rat brain mitochondria)
IT 312611-92-0
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(iron chelator VK-28 was poor inhibitor of monoamine oxidase-A and monoamine oxidase-B in rat brain mitochondria which was improved by its propargylamine derivs.)
OS.CITING REF COUNT: 33 THERE ARE 33 CAPLUS RECORDS THAT CITE THIS RECORD (33 CITINGS)
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

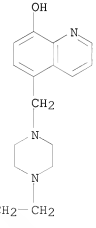
L6 ANSWER 17 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 141:33180 CA
TITLE: Ironing iron out in Parkinson's disease and other neurodegenerative diseases with iron chelators: A lesson from 6-hydroxydopamine and iron chelators, desferal and VK-28
AUTHOR(S): Youdim, Moussa B. H.; Stephenson, Galia; Ben Shachar, Dorit
CORPORATE SOURCE: Eve Topf and US National Parkinson Foundation Centers of Excellence for Neurodegenerative Diseases Research, and Department of Pharmacology, Technion-Rappaport Faculty of Medicine, Haifa, Israel
SOURCE: Annals of the New York Academy of Sciences (2004), 1012, 306-325
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. In Parkinson's disease (PD) and its neurotoxin-induced models, 6-hydroxydopamine (6-OHDA) and N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), significant accumulation of iron occurs in the substantia nigra pars compacta. The iron is thought to be in a labile pool, unbound to ferritin, and is thought to have a pivotal role to induce oxidative stress-dependent neurodegeneration of dopamine neurons via Fenton chemical The consequence of this is its interaction with H2O2 to generate the most reactive radical oxygen species, the hydroxyl radical. This scenario is supported by studies in both human and neurotoxin-induced

parkinsonism showing that disposition of H2O2 is compromised via depletion of glutathione (GSH), the rate-limiting cofactor of glutathione peroxide, the major enzyme source to dispose H2O2 as water in the brain. Further, radical scavengers have been shown to prevent the neurotoxic action of the above neurotoxins and depletion of GSH. However, our group was the first to demonstrate that the prototype iron chelator, desferal, is a potent neuroprotective agent in the 6-OHDA model. We have extended these studies and examined the neuroprotective effect of intracerebraventricular (ICV) pretreatment with the prototype iron chelator, desferal (1.3, 13, 134 μg), on ICV induced 6-OHDA (250 μg) lesion of striatal dopamine neurons. Desferal alone at the doses studied did not affect striatal tyrosine hydroxylase (TH) activity or dopamine (DA) metabolism All three pretreatment (30 min) doses of desferal prevented the fall in striatal and frontal cortex DA, dihydroxyphenylacetic acid, and homovalinic acid, as well as the left and right striatum TH activity and DA turnover resulting from 6-OHDA lesion of dopaminergic neurons. A concentration bell-shaped neuroprotective effect of desferal was observed in the striatum, with 13 μg being the most effective. Neither desferal nor 6-OHDA affected striatal serotonin, 5-hydroxyindole acetic acid, or noradrenaline. Desferal also protected against 6-OHDA-induced deficit in locomotor activity, rearing, and exploratory behavior (sniffing) in a novel environment. Since the lowest neuroprotective dose (1.3 μg) of desferal was 200 times less than 6-OHDA, its neuroprotective activity may not be attributed to interference with the neurotoxin activity, but rather iron chelation . These studies led us to develop novel brain-permeable iron chelators, the VK-28 series, with iron chelating and neuroprotective activity similar to desferal for ironing iron out from PD and other neurodegenerative diseases, such as Alzheimer's disease, Friedreich's ataxia, and Huntington's disease.

IT 312611-92-0, VK-28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(iron chelators desferal and VK-28 in Parkinson disease and other neurodegenerative diseases)

RN 312611-92-0 CA

CN 8-Quinolinol, 5-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]- (CA INDEX NAME)

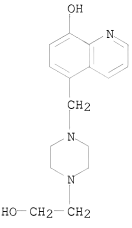


IT 312611-92-0, VK-28

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(iron chelators desferal and VK-28 in Parkinson disease and other neurodegenerative diseases)
OS.CITING REF COUNT: 64 THERE ARE 64 CAPLUS RECORDS THAT CITE THIS RECORD (64 CITINGS)
REFERENCE COUNT: 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 18 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 141:970 CA
TITLE: Neuroprotection by a novel brain permeable iron chelator, VK-28, against 6-hydroxydopamine lesion in rats
AUTHOR(S): Ben Shachar, Dorit; Kahana, Nava; Kampel, Vladimir; Warshawsky, Abraham; Youdim, Moussa B. H.
CORPORATE SOURCE: Laboratory of Psychobiology, Department of Psychiatry, Technion-Faculty of Medicine, Haifa, Israel
SOURCE: Neuropharmacology (2004), 46(2), 254-263
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Significant increase in iron occurs in the substantia nigra pars compacta of Parkinsonian subjects, and in 6-hydroxydopamine (6-OHDA) treated rats and monkeys. This increase in iron has been attributed to its release from ferritin and is associated with the generation of reactive oxygen species and the onset of oxidative stress-induced neurodegeneration. Several iron chelators with hydroxyquinoline backbone were synthesized and their ability to inhibit basal as well as iron-induced mitochondrial lipid peroxidn. was examined The neuroprotective potential of the brain permeable iron chelator, VK-28 (5-[4-(2-hydroxyethyl) piperazine-1-ylmethyl]-quinoline-8-ol), injected either intraventricularly (ICV) or i.p. (IP), to 6-OHDA lesioned rats was investigated. VK-28 inhibited both basal and Fe/ascorbate induced mitochondrial membrane lipid peroxidn., with an IC50 (12.7 μM) value comparable to that of the prototype iron chelator, desferal, which does not cross the blood brain barrier. At an ICV pretreatment dose as low as 1 μg, VK-28 was able to completely protect against ICV 6-OHDA (250 μg) induced striatal dopaminergic lesion, as measured by dopamine (DA), dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA) levels. IP injection of rats with VK-28 (1 and 5 mg/kg) daily for 10 and 7 days, resp., demonstrated significant neuroprotection against ICV 6-OHDA at the higher dose, with 68% protection against loss of dopamine at 5mg/kg dosage of VK-28. The present study is the first to show neuroprotection with a brain permeable iron chelator. The latter can have implications for the treatment of Parkinson's disease and other neurodegenerative diseases (Alzheimer's disease, Friedreich ataxia, aceruloplasminemia, Hallervorden Spatz syndrome) where abnormal iron accumulation in the brain is thought to be associated with the degenerative processes.
IT 312611-92-0, VK 28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotection by a novel brain permeable iron chelator, VK-28, against 6-hydroxydopamine lesion in rats)
RN 312611-92-0 CA

CN 8-Quinolinol, 5-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]- (CA INDEX NAME)



IT 312611-92-0, VK 28
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neuroprotection by a novel brain permeable iron chelator, VK-28, against 6-hydroxydopamine lesion in rats)

OS.CITING REF COUNT: 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS RECORD (31 CITINGS)

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 19 OF 20 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 140:423952 CA

TITLE: Preparation of neuroprotective iron chelators and pharmaceutical compositions comprising them

INVENTOR(S): Warshawsky, Abraham; Youdim, Moussa B. H.; Fridkin, Matitiyahu; Zheng, Hailin; Warshawsky, Rivka

PATENT ASSIGNEE(S): Technion Research and Development Foundation Ltd., Israel; Yeda Research and Development Co. Ltd.

SOURCE: PCT Int. Appl., 147 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004041151	A2	20040521	WO 2003-IL932	20031107
WO 2004041151	A3	20041028		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2505476	A1	20040521	CA 2003-2505476	20031107
AU 2003282337	A1	20040607	AU 2003-282337	20031107
AU 2003282337	B2	20090716		
EP 1565185	A2	20050824	EP 2003-773953	20031107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006515599 T		20060601	JP 2005-502148	20031107
US 2006023492 7	A1	20061019	US 2003-534357	20060221

PRIORITY APPLN. INFO.: US 2002-424313P P 20021107
US 2003-504126P P 20030922
WO 2003-IL932 W 20031107

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 140:423952

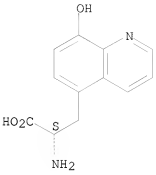
AB Novel iron chelators exhibiting neuroprotective and good transport properties are useful in iron chelation therapy for treatment of a disease, disorder or condition associated with iron overload and oxidative stress (e.g., a neurodegenerative or cerebrovascular disease or disorder, a neoplastic disease, hemochromatosis, thalassemia, a cardiovascular disease, diabetes, an inflammatory disorder, anthracycline cardiotoxicity, a viral infection, a protozoal infection, a yeast infection, retarding aging, and prevention and/or treatment of skin aging and skin protection against sunlight and/or UV light). The iron chelator function is provided by a 8-hydroxyquinoline, hydroxypyridinone or hydroxamate moiety, the neuroprotective function is imparted to the compound by a neuroprotective peptide, and a combined antiapoptotic and neuroprotective function by a propargyl group. The examples illustrate syntheses of compds. of the invention, e.g., Fmoc-KKC(HQ)L-NH2 (HQ is 8-hydroxyquinoline, Fmoc is fluorenylmethoxycarbonyl), for which iron-scavenging properties were assessed in human erythroleukemia K562 cells (shown graphically).

IT 72903-50-5P
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of neuroprotective iron chelators comprising peptide, hydroxyquinoline, and related moieties)

RN 72903-50-5 CA

CN 5-Quinolinepropanoic acid, α-amino-8-hydroxy-, (αS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



IT 72903-50-5P
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PUR (Purification or recovery); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of neuroprotective iron chelators comprising peptide, hydroxyquinoline, and related moieties)

IT 686722-50-9P
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of neuroprotective iron chelators comprising peptide, hydroxyquinoline, and related moieties)

IT 686722-51-0P 686722-52-1P
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of neuroprotective iron chelators comprising peptide, hydroxyquinoline, and related moieties)

IT 686722-49-6P
RL: BPN (Biosynthetic preparation); PUR (Purification or recovery); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of neuroprotective iron chelators comprising peptide, hydroxyquinoline, and related moieties)

IT 23279-45-0P 686722-47-4P 686722-48-5P
686722-54-3P 686722-58-7P 686722-59-8P
686722-60-1P 686722-61-2P 686722-62-3P
686722-63-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of neuroprotective iron chelators comprising peptide, hydroxyquinoline, and related moieties)

IT 686722-53-2P 686722-77-0P 686722-82-7P
686722-84-9P 686722-86-1P 686722-90-7P
686722-91-8P 686722-94-1P 686722-95-2P
686722-96-3P 686722-97-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of neuroprotective iron chelators
comprising peptide, hydroxyquinoline, and related moieties)
IT 312611-92-0 686723-14-8 686723-15-9
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of neuroprotective iron chelators
comprising peptide, hydroxyquinoline, and related moieties)
OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 20 OF 20 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 134:37041 CA
TITLE: Pharmaceutical compositions comprising iron chelators for the treatment of neurodegenerative disorders, some novel iron chelators, and compound preparation
INVENTOR(S): Warshawsky, Abraham; Youdim, Moussa B. H.; Ben-Shachar, Dorit
PATENT ASSIGNEE(S): Yeda Research and Development Co. Ltd., Israel; Technion Research and Development Foundation Ltd.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000074664	A2	20001214	WO 2000-IL332	20000607
WO 2000074664	A3	20010927		
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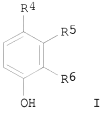
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2374317	A1	20001214	CA 2000-2374317	20000607
CA 2374317	C	20091201		
EP 1189606	A2	20020327	EP 2000-935453	20000607
EP 1189606	B1	20070815		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
AU 769582	B2	20040129	AU 2000-50992	20000607
AT 369858	T	20070915	AT 2000-935453	20000607
IL 146944	A	20080120	IL 2000-146944	20000607
US 6855711	B1	20050215	US 2002-9300	20020513
PRIORITY APPLN. INFO.:			IL 1999-130324 A	19990607
			WO 2000-IL332 W	20000607

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 134:37041
GI



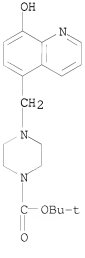
I

AB The invention discloses the use of CH2[(R3CH2)2N]CH[N(CH2R3)2](CH2)nCONR1R2 [R1 = H, hydrocarbyl; R2 = hydrophobic radical; R3 = 3-(C2-C6)acyl-4-hydroxyphenyl, 3-hydroxyimino(C2-C6)-alkyl-4-hydroxyphenyl, COOZ (Z = H, (C1-C6)alkyl, aryl or Ar(C1-C6)alkyl); n= 1-20], and of I [R4 = (C1-C6)acyl, nitro(C1-C6)alkyl, cyano(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkyl, CH2NR7R8; R7, R8, = H, (C1-C6)alkyl, or together with N atom form (un)saturated 5-7-membered ring optionally containing further heteroatom selected from N, O or S, further N atom optionally substituted; either R5 = H and R6 = (C2-C6) acyl, hydroxyimino(C2-C6)alkyl, or R5 and R6 together with the Ph ring form a quinoline, a 1,2,3,4-tetrahydroquinoline or a perhydroquinoline ring], for the preparation of pharmaceutical compns. for the treatment of Parkinson's disease or stroke.

IT 312611-95-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(iron chelators for treatment of neurodegenerative disorders, and compound preparation)

RN 312611-95-3 CA

CN 1-Piperazinecarboxylic acid, 4-[(8-hydroxy-5-quinolinyl)methyl]-, 1,1-dimethylethyl ester (CA INDEX NAME)



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IT   312611-95-3P 312611-97-5P
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT
     (Reactant or reagent); USES (Uses)
        (iron chelators for treatment of neurodegenerative
        disorders, and compound preparation)
IT   22505-80-2P 22506-13-4P 41455-83-8P
     57434-83-0P 312611-89-5P 312611-90-8P
     312611-91-9P 312611-92-0P 312611-93-1P
     312611-94-2P 312611-96-4P 312611-98-6P
     312611-99-7P 312612-02-5P 312612-03-6P
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (iron chelators for treatment of neurodegenerative
        disorders, and compound preparation)
OS.CITING REF COUNT:     9     THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD
                               (9 CITINGS)
REFERENCE COUNT:         3     THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> (iron chelator) and neuroprotective
(IRON IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s (iron chelator) and neuroprotective
       1141221 IRON
         13400 CHELATOR
          2489 IRON CHELATOR
                 (IRON(W)CHELATOR)
         28201 NEUROPROTECTIVE
L7          77 (IRON CHELATOR) AND NEUROPROTECTIVE

=> d his

     (FILE 'HOME' ENTERED AT 14:20:56 ON 25 FEB 2010)

     FILE 'REGISTRY' ENTERED AT 14:21:10 ON 25 FEB 2010
L1               STRUCTURE UPLOADED
L2            39 S L1 SAM
L3           578 S L1 FULL

     FILE 'CA' ENTERED AT 14:21:49 ON 25 FEB 2010
L4           258 S L3
L5          6630 S IRON CHELAT?
L6            20 S L5 AND L4
L7            77 S (IRON CHELATOR) AND NEUROPROTECTIVE

=> s l7 not l6
L8           61 L7 NOT L6

=> s l8 an dpy<2002
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MISSING OPERATOR L8 AN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l8 and py<2002
      21121347 PY<2002
L9           15 L8 AND PY<2002

=> d ibib abs abs 1-15

L9   ANSWER 1 OF 15  CA  COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER:        135:225196  CA
TITLE:                   Gene expression analysis in
                         N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mice
                         model of Parkinson's disease using cDNA microarray:
                         effect of R-apomorphine
AUTHOR(S):               Grunblatt, Edna; Mandel, Silvia; Maor, Gila; Youdim,
                         Moussa B. H.
CORPORATE SOURCE:        Technion Faculty of Medicine, Bruce Rappaport Family
                         Research Institute, Department of Pharmacology, Eve
                         Topf and US National Parkinson's Foundation Centers
                         for Neurodegenerative Diseases, Haifa, Israel
SOURCE:                  Journal of Neurochemistry (2001), 78(1),
                         1-12
                         CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER:               Blackwell Science Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   To establish the possible roles of oxidative stress, inflammatory
     processes and other unknown mechanisms in neurodegeneration, we
     investigated brain gene alterations in
     N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice model of
     Parkinson's disease using Atlas mouse cDNA expression array membrane.  The
     expression of 51 different genes involved in oxidative stress,
     inflammation, glutamate and neurotrophic factors pathways as well as in
     still undefined processes, such as cell cycle regulators and signal
     transduction mols., was differentially affected by the treatment.  The
     present study indicates the involvement of an addnl. cascade of events
     that might act in parallel to oxidative stress and inflammation to
     converge eventually into a common pathway leading to neurodegeneration.
     The attenuation of these gene changes by R-apomorphine, an iron
     chelator-radical scavenger drug, supports our previous findings in
     vivo where R-apomorphine was neuroprotective.
AB   To establish the possible roles of oxidative stress, inflammatory
     processes and other unknown mechanisms in neurodegeneration, we
     investigated brain gene alterations in
     N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice model of
     Parkinson's disease using Atlas mouse cDNA expression array membrane.  The
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     transduction mols., was differentially affected by the treatment.  The
     present study indicates the involvement of an addnl. cascade of events
     that might act in parallel to oxidative stress and inflammation to
     converge eventually into a common pathway leading to neurodegeneration.
     The attenuation of these gene changes by R-apomorphine, an iron
     chelator-radical scavenger drug, supports our previous findings in
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vivo where R-apomorphine was neuroprotective.
OS.CITING REF COUNT: 113 THERE ARE 113 CAPLUS RECORDS THAT CITE THIS RECORD (113 CITINGS)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 15 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 135:86375 CA
TITLE: Iron chelating, antioxidant and cytoprotective properties of dopamine receptor agonist; apomorphine
AUTHOR(S): Youdim, M. B. H.; Gassen, M.; Gross, A.; Mandel, S.; Grunblatt, E.
CORPORATE SOURCE: Department of Pharmacology, Eve Topf and National Parkinson's Foundation Centers, Bruce Rappaport Family Research Institute, Faculty of Medicine, Haifa, Israel
SOURCE: Advances in Research on Neurodegeneration (2000), 7(7th International Winter Conference on Neurodegeneration, 1999), 83-96
CODEN: ARNEFX; ISSN: 1068-719X
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 30 refs. There have been many attempts to discover neuroprotective drugs for the treatment of Parkinson's disease (PD). Many of these compds. either do not cross the blood brain barrier or are not very effective in the 6-hydroxydopamine or MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) models of PD. We have examined several compds. including dopamine receptor agonist bromocriptine, lisuride, pergolide and R-apomorphine for their neuroprotective action against the above neurotoxins in PC12 and dopamine neuroblastoma cell lines in culture and in vivo. R-apomorphine exhibited relatively potent neuroprotective action in vitro, cell culture and in vivo as a radical scavenger and iron chelator, because of its catechol structure. The recent clin. trials with apomorphine, where parkinsonian subjects can be weaned off L-dopa would suggest that this drug either exerts a neuroprotective action or that continuous sustained stimulation of dopamine receptor may be responsible for its unusual pharmacol. activity. Apomorphine has a far more broad neuroprotective activity in the various models as compared with l-selegiline and may therefore be an ideal drug to study neuroprotection in parkinsonian subjects with the use of PET or SPECT.
AB A review with 30 refs. There have been many attempts to discover neuroprotective drugs for the treatment of Parkinson's disease (PD). Many of these compds. either do not cross the blood brain barrier or are not very effective in the 6-hydroxydopamine or MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) models of PD. We have examined several compds. including dopamine receptor agonist bromocriptine, lisuride, pergolide and R-apomorphine for their neuroprotective action against the above neurotoxins in PC12 and dopamine neuroblastoma cell lines in culture and in vivo. R-apomorphine exhibited relatively potent neuroprotective action in vitro, cell culture and in vivo as a radical scavenger and iron chelator, because of its catechol structure. The recent clin. trials with apomorphine, where parkinsonian subjects can be weaned off L-dopa would suggest that this drug either exerts a neuroprotective action or that continuous sustained stimulation of dopamine receptor may be responsible for its unusual pharmacol. activity. Apomorphine has a far more broad

neuroprotective activity in the various models as compared with 1-selegiline and may therefore be an ideal drug to study neuroprotection in parkinsonian subjects with the use of PET or SPECT.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 15 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 134:36618 CA

TITLE: Ironing-out mechanisms of neuronal injury under hypoxic-ischemic conditions and potential role of iron chelators as neuroprotective agents

AUTHOR(S): Sorond, Farzaneh A.; Ratan, Rajiv R.

CORPORATE SOURCE: Department of Neurology, Harvard Medical School and Beth Israel-Deaconess Medical Center, Boston, MA, 02115, USA

SOURCE: Antioxidants & Redox Signaling (2000), 2(3), 421-436
CODEN: ARSIF2; ISSN: 1523-0864

PUBLISHER: Mary Ann Liebert

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with many refs. Iron is the most abundant transition metal in the brain, where it functions as an important cofactor in a host of vital metabolic processes and plays an absolutely essential role in cell viability. Free iron is also very toxic when present in high concns., thus placing this essential metal at the core of neurotoxic injury in a number of neurol. disorders. The pivotal role of iron in cellular homeostasis, including its latent toxicity, necessitates a tight regulation of iron metabolism Oxygen and iron appear to play an important role in iron homeostasis. They appear to exert their homeostatic role by modulating the proteins involved in a complex interplay between iron sensing, transport, and storage. These key regulatory proteins include ferritin (intracellular storage), transferrin (extracellular transport), transferrin receptor, and iron regulatory protein (sensor of intracellular iron concentration). The interplay of iron and oxygen is most intriguing in the setting of stroke, where hypoxia and free iron appear to interact in causing the subsequent neuronal death.

AB A review with many refs. Iron is the most abundant transition metal in the brain, where it functions as an important cofactor in a host of vital metabolic processes and plays an absolutely essential role in cell viability. Free iron is also very toxic when present in high concns., thus placing this essential metal at the core of neurotoxic injury in a number of neurol. disorders. The pivotal role of iron in cellular homeostasis, including its latent toxicity, necessitates a tight regulation of iron metabolism Oxygen and iron appear to play an important role in iron homeostasis. They appear to exert their homeostatic role by modulating the proteins involved in a complex interplay between iron sensing, transport, and storage. These key regulatory proteins include ferritin (intracellular storage), transferrin (extracellular transport), transferrin receptor, and iron regulatory protein (sensor of intracellular iron concentration). The interplay of iron and oxygen is most intriguing in the setting of stroke, where hypoxia and free iron appear to interact in causing the subsequent neuronal death.

OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 106 THERE ARE 106 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 15 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 133:133599 CA
TITLE: Neuronal apoptosis induced by pharmacological concentrations of 3-hydroxykynurenine: characterization and protection by dantrolene and Bcl-2 overexpression
AUTHOR(S): Wei, Huafeng; Leeds, Peter; Chen, Ren-Wu; Wei, Wenlin; Leng, Yan; Bredesen, Dale E.; Chuang, De-Maw
CORPORATE SOURCE: Section on Molecular Neurobiology, Biological Psychiatry Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, 20892-1272, USA
SOURCE: Journal of Neurochemistry (2000), 75(1), 81-90
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have studied neurotoxicity induced by pharmacol. concns. of 3-hydroxykynurenine (3-HK), an endogenous toxin implicated in certain neurodegenerative diseases, in cerebellar granule cells, PC12 pheochromocytoma cells, and GT1-7 hypothalamic neurosecretory cells. In all three cell types, the toxicity was induced in a dose-dependent manner by 3-HK at high micromolar concns. and had features characteristic of apoptosis, including chromatin condensation and internucleosomal DNA cleavage. In cerebellar granule cells, the 3-HK neurotoxicity was unaffected by xanthine oxidase inhibitors but markedly potentiated by superoxide dismutase and its heme-like mimetic, MnTBAP [manganese(III) tetrakis(benzoic acid)porphyrin chloride]. Catalase blocked 3-HK neurotoxicity in the absence and presence of superoxide dismutase or MnTBAP. The formation of H2O2 was demonstrated in PC12 and GT1-7 cells treated with 3-HK, by measuring the increase in the fluorescent product, 2',7'-dichlorofluorescein. In both PC12 and cerebellar granule cells, inhibitors of the neutral amino acid transporter that mediates the uptake of 3-HK failed to block 3-HK toxicity. However, their toxicity was slightly potentiated by the iron chelator, deferoxamine. Taken together, our results suggest that neurotoxicity induced by pharmacol. concns. of 3-HK in these cell types is mediated primarily by H2O2, which is formed most likely by auto-oxidation of 3-HK in extracellular compartments. 3-HK-induced death of PC12 and GT1-7 cells was protected by dantrolene, an inhibitor of calcium release from the endoplasmic reticulum. The protection by dantrolene was associated with a marked increase in the protein level of Bcl-2, a prominent antiapoptotic gene product. Moreover, overexpression of Bcl-2 in GT1-7 cells elicited by gene transfection suppressed 3-HK toxicity. Thus, dantrolene may elicit its neuroprotective effects by mechanisms involving up-regulation of the level and function of Bcl-2 protein.
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OS.CITING REF COUNT: 42 THERE ARE 42 CAPLUS RECORDS THAT CITE THIS RECORD (43 CITINGS)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 15 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 133:622 CA

TITLE: The neuroprotective effect of deferoxamine in the hypoxic-ischemic immature mouse brain

AUTHOR(S): Sarco, D. P.; Becker, J.; Palmer, C.; Sheldon, R. A.; Ferriero, D. M.

CORPORATE SOURCE: Departments of Neurology and Pediatrics, Neonatal Brain Disorders Laboratory, University of California-San Francisco, San Francisco, CA, USA

SOURCE: Neuroscience Letters (2000), 282(1,2), 113-116
CODEN: NELED5; ISSN: 0304-3940

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The iron chelator deferoxamine is efficacious in ameliorating hypoxic-ischemic brain injury in some models, perhaps by decreasing oxidative stress. Transgenic copper/zinc superoxide dismutase-1 (SOD1) overexpression in neonatal mice increases brain injury after hypoxia-ischemia compared to non-transgenic wild type littermates because of increased oxidative stress. A neonatal mouse model of hypoxia-ischemia was used to examine histopathol. damage, iron histochem. and free iron concentration in the brains of SOD1 transgenic and non-transgenic littermates. Deferoxamine significantly decreased injury in non-transgenics compared to controls with a trend toward neuroprotection in the transgenics. There was no difference in free iron concns. in the brains of SOD1 overexpressors or non-transgenics. Deferoxamine may

protect the neonatal brain by a number of antioxidant mechanisms including iron chelation, enhancement of stress gene expression, or induction of other factors responsible for neuroprotection.

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OS.CITING REF COUNT: 32 THERE ARE 32 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 15 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 132:117462 CA

TITLE: Effects of stobadine, melatonin, and other antioxidants on hypoxia/reoxygenation-induced synaptic transmission failure in rat hippocampal slices

AUTHOR(S): Vlkolinsky, Roman; Stolc, Svorad

CORPORATE SOURCE: Institute of Experimental Pharmacology, Slovak Academy of Sciences, Bratislava, SK-842 16, Slovakia

SOURCE: Brain Research (1999), 850(1,2), 118-126
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In vitro reversible ischemia was simulated with rat hippocampal slices in order to test the neuroprotective activity of selected antioxidants with emphasis on the pyridoindole stobadine. Slices were exposed to hypoxia (HYP) combined with lowered D-glucose concentration to induce synaptic transmission (ST) failure, which turned out to be irreversible in approx. 80%-100% of slices during reoxygenation (ROX). The amplitude of population spikes (PoS) evoked transsynaptically by elec. stimulation of Schaffer collaterals and recorded in CA1 neurons was the parameter of ST. Pretreatment of slices with stobadine dissolved in slice superfusion media (1 to 100 μM) improved ST recovery after 20-min tissue ROX. Stobadine decreased the number of irreversibly damaged slices and increased the average amplitude of PoS during tissue ROX. The concentration-response relationship of protective activity was bell-shaped, with maximum at 3-30 μM. Moreover, the half-time of PoS decay (t1/2) during HYP was significantly delayed in stobadine treated groups (10 to 100 μM). The neurohormone melatonin (30 to 100 μM) and 21-aminosteroid U-74389G (10 μM) revealed similar protective activity on ST recovery and on t1/2 during HYP. Trolox (200 μM) improved the PoS recovery, yet it had no effect on t1/2. The iron chelator deferoxamine (250 and 500 μM) had no protective effects at all. α-Tocopherol administered to animals

orally (200 mg/kg for 10 days) only marginally improved the PoS recovery. Comparing the protective effect of compds. tested on PoS recovery, we assume the following rank order of potency: U-74389G > stobadine > melatonin >> trolox. Our findings suggest that stobadine as well as trolox, U-74389G and melatonin, antioxidants with remarkably different chemical structures, exerted neuroprotective activity, probably determined by antioxidative properties of these compds. Moreover, stobadine, U-74389G, and melatonin were able to delay the early ST decay during HYP, which might indicate improved energetic state of neurons in the treated tissue. The study supports the notion about the neuroprotective activity of certain antioxidants.

AB In vitro reversible ischemia was simulated with rat hippocampal slices in order to test the neuroprotective activity of selected antioxidants with emphasis on the pyridoindole stobadine. Slices were exposed to hypoxia (HYP) combined with lowered D-glucose concentration to induce synaptic transmission (ST) failure, which turned out to be irreversible in approx. 80%-100% of slices during reoxygenation (ROX). The amplitude of population spikes (PoS) evoked transsynaptically by elec. stimulation of Schaffer collaterals and recorded in CA1 neurons was the parameter of ST. Pretreatment of slices with stobadine dissolved in slice superfusion media (1 to 100 μM) improved ST recovery after 20-min tissue ROX. Stobadine decreased the number of irreversibly damaged slices and increased the average amplitude of PoS during tissue ROX. The concentration-response relationship of protective activity was bell-shaped, with maximum at 3-30 μM. Moreover, the half-time of PoS decay (t1/2) during HYP was significantly delayed in stobadine treated groups (10 to 100 μM). The neurohormone melatonin (30 to 100 μM) and 21-aminosteroid U-74389G (10 μM) revealed similar protective activity on ST recovery and on t1/2 during HYP. Trolox (200 μM) improved the PoS recovery, yet it had no effect on t1/2. The iron chelator deferoxamine (250 and 500 μM) had no protective effects at all. α-Tocopherol administered to animals orally (200 mg/kg for 10 days) only marginally improved the PoS recovery. Comparing the protective effect of compds. tested on PoS recovery, we assume the following rank order of potency: U-74389G > stobadine > melatonin >> trolox. Our findings suggest that stobadine as well as trolox, U-74389G and melatonin, antioxidants with remarkably different chemical structures, exerted neuroprotective activity, probably determined by antioxidative properties of these compds. Moreover, stobadine, U-74389G, and melatonin were able to delay the early ST decay during HYP, which might indicate improved energetic state of neurons in the treated tissue. The study supports the notion about the neuroprotective activity of certain antioxidants.

OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 15 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 132:44853 CA

TITLE: Protection from oxidative stress-induced apoptosis in cortical neuronal cultures by iron chelators is associated with enhanced DNA binding of hypoxia-inducible factor-1 and ATF-1/CREB and increased expression of glycolytic enzymes, p21waf1/cip1, and erythropoietin

AUTHOR(S): Zaman, Khalequz; Rvu, Hoon; Hall, David; O'Donovan,

Kevin; Lin, Kuo-I.; Miller, Matthew P.; Marquis, John C.; Baraban, Jay M.; Semenza, Gregg L.; Ratan, Rajiv R.
CORPORATE SOURCE: Department of Neurology, Harvard Medical School and The Beth Israel Deaconess Medical Center, Boston, MA, 02115, USA
SOURCE: Journal of Neuroscience (1999), 19(22), 9821-9830
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Iron chelators are pluripotent neuronal antiapoptotic agents that have been shown to enhance metabolic recovery in cerebral ischemia models. The precise mechanism(s) by which these agents exert their effects remains unclear. Recent studies have demonstrated that iron chelators activate a hypoxia signal transduction pathway in non-neuronal cells that culminates in the stabilization of the transcriptional activator hypoxia-inducible factor-1 (HIF-1) and increased expression of gene products that mediate hypoxic adaptation. We examined the hypothesis that iron chelators prevent oxidative stress-induced death in cortical neuronal cultures by inducing expression of HIF-1 and its target genes. We report that the structurally distinct iron chelators deferoxamine mesylate and mimosine prevent apoptosis induced by glutathione depletion and oxidative stress in embryonic cortical neuronal cultures. The protective effects of iron chelators are correlated with their ability to enhance DNA binding of HIF-1 and activating transcription factor 1(ATF-1)/cAMP response element-binding protein (CREB) to the hypoxia response element in cortical cultures and the H19-7 hippocampal neuronal cell line. We show that mRNA, protein, and/or activity levels for genes whose expression is known to be regulated by HIF-1, including glycolytic enzymes, p21waf1/cip1, and erythropoietin, are increased in cortical neuronal cultures in response to iron chelator treatment. Finally, we demonstrate that cobalt chloride, which also activates HIF-1 and ATF-1/CREB in cortical cultures, also prevents oxidative stress-induced death in these cells. Altogether, these results suggest that iron chelators exert their neuroprotective effects, in part, by activating a signal transduction pathway leading to increased expression of genes known to compensate for hypoxic or oxidative stress.
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regulated by HIF-1, including glycolytic enzymes, p21waf1/cip1, and erythropoietin, are increased in cortical neuronal cultures in response to iron chelator treatment. Finally, we demonstrate that cobalt chloride, which also activates HIF-1 and ATF-1/CREB in cortical cultures, also prevents oxidative stress-induced death in these cells. Altogether, these results suggest that iron chelators exert their neuroprotective effects, in part, by activating a signal transduction pathway leading to increased expression of genes known to compensate for hypoxic or oxidative stress.

OS.CITING REF COUNT: 155 THERE ARE 155 CAPLUS RECORDS THAT CITE THIS RECORD (155 CITINGS)

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 15 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 131:209048 CA

TITLE: Potent neuroprotective and antioxidant activity of apomorphine in MPTP and 6-hydroxydopamine induced neurotoxicity

AUTHOR(S): Grunblatt, E.; Mandel, S.; Gassen, M.; Youdim, M. B. H.

CORPORATE SOURCE: Technion - Faculty of Medicine, Eve Topf and U.S. National Parkinson's Foundation Centers for, Haifa, Israel

SOURCE: Advances in Research on Neurodegeneration (1999), 6(International Winter Conference on Neurodegeneration, 6th, 1997), 57-70
CODEN: ARNEFX; ISSN: 1068-719X

PUBLISHER: Springer-Verlag Wien

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Apomorphine is a potent radical scavenger and iron chelator. In vitro apomorphine acts as a potent iron chelator and radical scavenger with IC50 of 0.3μM for iron (2.5μM) induced lipid peroxidn. in rat brain mitochondrial preparation, and it inhibits mice striatal MAO-A and MAO-B activities with IC50 values of 93μM and 241μM. Apomorphine (1-10μM) protects rat pheochromocytoma (PC12) cells from 6-hydroxydopamine (150μM) and H2O2 (0.6mM) induced cytotoxicity and cell death. The neuroprotective property of (R)-apomorphine, a dopamine D1-D2 receptor agonist, has been studied in the MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of Parkinson's disease. (R)-apomorphine (5-10 mg/kg, s.c.) pretreatment in C57BL mice, protects against MPTP (24 mg/kg, I.P) induced loss of nigrostriatal dopamine neurons, as indicated by striatal dopamine content, tyrosine hydroxylase content and tyrosine hydroxylase activity. It is suggested that the neuroprotective effect of (R)-apomorphine against MPTP neurotoxicity derives from its radical scavenging and MAO inhibitory actions and not from its agonistic activity, since the mechanism of MPTP dopaminergic neurotoxicity involves the generation of oxygen radical species induced-oxidative stress.

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(0.6mM) induced cytotoxicity and cell death. The neuroprotective property of (R)-apomorphine, a dopamine D1-D2 receptor agonist, has been studied in the MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of Parkinson's disease. (R)-apomorphine (5-10 mg/kg, s.c.) pretreatment in C57BL mice, protects against MPTP (24 mg/kg, I.P) induced loss of nigrostriatal dopamine neurons, as indicated by striatal dopamine content, tyrosine hydroxylase content and tyrosine hydroxylase activity. It is suggested that the neuroprotective effect of (R)-apomorphine against MPTP neurotoxicity derives from its radical scavenging and MAO inhibitory actions and not from its agonistic activity, since the mechanism of MPTP dopaminergic neurotoxicity involves the generation of oxygen radical species induced-oxidative stress.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 15 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 128:252874 CA

ORIGINAL REFERENCE NO.: 128:49927a,49930a

TITLE: The iron chelator desferrioxamine protects against MPP+ neurotoxicity

AUTHOR(S): Matarredona, E. R.; Santiago, M.; Machado, A.; Cano, J.

CORPORATE SOURCE: Departamento de Bioquimica, Bromatologia y Toxicologia, Facultad de Farmacia, Universidad de Sevilla, Spain

SOURCE: Neurochemistry: Cellular, Molecular and Clinical Aspects, [Proceedings of the European Society for Neurochemistry Meeting], 11th, Groningen, June 15-20, 1996 (1997), Meeting Date 1996, 309-313. Editor(s): Teelken, Albert; Korf, Jaap. Plenum: New York, N. Y. CODEN: 65STAK

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Previous work has suggested the possible importance of iron in a proposed oxidative stress mechanisms of MPP+ neurotoxicity and the potential neuroprotective action of iron chelators. This study investigated the effect of the iron chelator desferrioxamine (DES) on MPP+ neurotoxicity. MPP+ was perfused with or without DES in the corpus striatum of rats followed by another perfusion of MPP+ 24 h later. DES attenuated MPP+ neurotoxicity, measured by a reduction in dopamine output, in the 1 mM to 10 nM range. Co-perfusion of iron 20 mM with DES 10 nM abolished the DES 10 nM effect. The authors conclude that desferrioxamine protects against MPP+ neurotoxicity in rat corpus striatum, and that this protection is produced by its iron chelator capability.

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protects against MPP+ neurotoxicity in rat corpus striatum, and that this protection is produced by its iron chelator capability.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 15 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 128:269 CA
ORIGINAL REFERENCE NO.: 128:59a
TITLE: Involvement of iron in MPP+ toxicity in substantia nigra: protection by desferrioxamine
AUTHOR(S): Matarredona, Esperanza R.; Santiago, Marti; Cano, Josefina; Machado, Alberto
CORPORATE SOURCE: Departamento de Bioquimica, Bromatologia y Toxicologia, Facultad de Farmacia, Universidad de Sevilla, 41012-, Seville, Spain
SOURCE: Brain Research (1997), 773(1,2), 76-81
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Desferrioxamine (DES) protective effect against 1-methyl-4-phenylpyridinium (MPP+) toxicity was evaluated by microdialysis in the substantia nigra. DES (1 μM to 10 mM) co-perfused with MPP+ (2.5 mM) on day 1, produced on day 2 a higher dopamine extracellular output after perfusion of MPP+ than in control-MPP+ perfusion expts., in which no DES was administered on day 1. Both Ringer's perfusion alone (control-Ringer) and co-perfusion of DES (10 mM) with MPP+ (2.5 mM) on day 1 produced on day 2 similar increases in dopamine extracellular output after a second MPP+ perfusion. In the control-Ringer experiment, note that the MPP+ on day 2 is the first MPP+ perfusion. Perfusion of FeCl3 (200 μM) along with MPP+ (2.5 mM) and DES (100 μM) on day 1 completely abolished on day 2 the neuroprotective effect found with MPP+ (2.5 mM) and DES (100 μM). The ability of DES to protect against MPP+ toxicity may indicate a therapeutic strategy in the treatment of diseases when iron is implicated.
AB Desferrioxamine (DES) protective effect against 1-methyl-4-phenylpyridinium (MPP+) toxicity was evaluated by microdialysis in the substantia nigra. DES (1 μM to 10 mM) co-perfused with MPP+ (2.5 mM) on day 1, produced on day 2 a higher dopamine extracellular output after perfusion of MPP+ than in control-MPP+ perfusion expts., in which no DES was administered on day 1. Both Ringer's perfusion alone (control-Ringer) and co-perfusion of DES (10 mM) with MPP+ (2.5 mM) on day 1 produced on day 2 similar increases in dopamine extracellular output after a second MPP+ perfusion. In the control-Ringer experiment, note that the MPP+ on day 2 is the first MPP+ perfusion. Perfusion of FeCl3 (200 μM) along with MPP+ (2.5 mM) and DES (100 μM) on day 1 completely abolished on day 2 the neuroprotective effect found with MPP+ (2.5 mM) and DES (100 μM). The ability of DES to protect against MPP+ toxicity may indicate a therapeutic strategy in the treatment of diseases when iron is implicated.
OS.CITING REF COUNT: 14 THERE ARE 14 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)

L9 ANSWER 11 OF 15 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 127:272674 CA
ORIGINAL REFERENCE NO.: 127:53089a,53092a

TITLE: Desferrioxamine and vitamin E protect against iron and MPTP-induced neurodegeneration in mice
AUTHOR(S): Lan, J.; Jiang, D. H.
CORPORATE SOURCE: Tianjin Neurological Institute, Tianjin Medical University Hospital, Peop. Rep. China
SOURCE: Journal of Neural Transmission (1997), 104(4-5), 469-481
CODEN: JNTRF3; ISSN: 0300-9564
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To elucidate the neuroprotective effects of the iron chelator desferrioxamine (DFO) and the antioxidant vitamin E on excessive iron-induced free radical damage, a chronic iron-loaded mice model was established. The relation between striatal iron content, oxidized to reduced glutathione ratio, hydroxyl radical (OH•) levels and dopamine concns. were observed in DFO or vitamin E pretreated iron-loaded/1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated C57BL/6 mice. The results demonstrated that both DFO and vitamin E inhibit the iron accumulation and thus reverses the increase in oxidized glutathione (GSSG), oxidized to reduced glutathione ratios, OH• and lipid peroxidn. levels. The striatal dopamine concentration was elevated to normal value. Our data suggested that: (1) iron may induce neuronal damage and thus excessive iron in the brain may contribute to the neuronal loss in PD; (2) iron chelators and antioxidants may serve as potential therapeutic agents in retarding the progression of neurodegeneration.
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OS.CITING REF COUNT: 77 THERE ARE 77 CAPLUS RECORDS THAT CITE THIS RECORD (79 CITINGS)
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 15 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 127:174848 CA
ORIGINAL REFERENCE NO.: 127:33861a,33864a
TITLE: Dopamine-melanin induces apoptosis in PC12 cells; possible implications for the etiology of Parkinson's disease
AUTHOR(S): Offen, Daniel; Ziv, Ilan; Barzilai, Ari; Gorodin, Svetlana; Glater, Elizabeth; Hochman, Ayala; Melamed, Eldad
CORPORATE SOURCE: Department of Neurology, Felsenstein Medical Research Center, Tel-Aviv University, Tel-Aviv, 49100, Israel

SOURCE: Neurochemistry International (1997), 31(2), 207-216
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The function of neuromelanin (NM), the oxidized dopamine (DA) polymer, within the DA-producing cells in the human and primate substantia nigra (SN), is still an enigma. Some studies show that the vulnerability of nigral neurons in Parkinson's disease is correlated to their toxic NM content, while others suggest that it contributes to cellular protection. The authors showed recently that DA, the endogenous nigral neurotransmitter, triggers apoptosis, an active program of cellular self-destruction, in neuronal cultures. In the present study, the authors exposed cells to synthetic dopamine-melanin (DA-M) and analyzed the cellular and genetic changes. The authors found that exposure of PC12 cells to DA-M (0.5 mg/mL for 24 h) caused 50% cell death, as indicated by trypan blue exclusion assay and 3H-thymidine incorporation. Gel electrophoresis DNA anal. of PC12 cells treated with DA-M showed the typical apoptotic DNA ladder, indicating inter-nucleosomal DNA degradation The DNA fragmentation also was visualized histochem. in situ by DNA end-labeling staining (the TUNEL method). The FeCl2 (0.05 mM) significantly increased DA-M toxicity, while desferrioxamine, an iron chelator, totally abolished the additive toxicity of iron. The contribution of oxidative stress in this model of DA-M-induced cell death was examined using various antioxidants. In contrast to DA, inhibition of DA-M toxicity by reduced glutathione (GSH), N-acetylcysteine, catalase and Zn/Cu superoxide dismutase (SOD) was very limited. In conclusion, the authors found that DA-M may induce typical apoptotic death in PC12 cells. The authors' findings support a possible role of NM in the vulnerability of the dopaminergic neural degeneration in Parkinson's disease. The differential protective effect by antioxidants against toxicity of DA and DA-M may have implications for future neuroprotective therapeutic approaches for this common neurol. disorder.
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OS.CITING REF COUNT: 65 THERE ARE 65 CAPLUS RECORDS THAT CITE THIS RECORD (65 CITINGS)

L9 ANSWER 13 OF 15 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 126:181231 CA
ORIGINAL REFERENCE NO.: 126:34849a,34852a
TITLE: Neuroprotective effect of the iron chelator desferrioxamine against MPP+ toxicity on striatal dopaminergic terminals
AUTHOR(S): Santiago, M.; Matarredona, E. R.; Granero, L.; Cano, J.; Machado, A.
CORPORATE SOURCE: Departamento de Bioquimica, Bromatologia y Toxicologia, Facultad de Farmacia, Universidad de Sevilla, Seville, Spain
SOURCE: Journal of Neurochemistry (1997), 68(2), 732-738
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Microdialysis was used to evaluate the effect of desferrioxamine (DES) against 1-methyl-4-phenylpyridinium (MPP+) toxicity. The presence of DES (40 fmol-40 nmol/15 min for a total of 90 min) in the Ringer solution, coperfused with MPP+ (40 nmol/15 min) on day 1, produced on day 2 a higher extracellular dopamine output after perfusion of MPP+ than in control MPP+ perfusion expts., in which no DES was administered on day 1. Both Ringer perfusion alone (control Ringer) and coperfusion of 40 nmol DES with 40 nmol MPP+ on day 1 produced on day 2 similar increases in extracellular dopamine output after a second MPP+ perfusion. In the control Ringer experiment, note that the MPP+ on day 2 is the first MPP+ perfusion. Perfusion of 800 fmol FeCl3/15 min along with 40 nmol MPP+ and 400 fmol DES on day 1 completely abolished on day 2 the neuroprotective effect found with 40 nmol MPP+ and 400 fmol DES; 800 fmol FeCl3 did not increase the neurotoxic effect of 40 nmol MPP+ perfusion. The ability of DES to protect against MPP+ toxicity may indicate a therapeutic strategy in the treatment of diseases when iron is implicated.

AB Microdialysis was used to evaluate the effect of desferrioxamine (DES) against 1-methyl-4-phenylpyridinium (MPP+) toxicity. The presence of DES (40 fmol-40 nmol/15 min for a total of 90 min) in the Ringer solution, coperfused with MPP+ (40 nmol/15 min) on day 1, produced on day 2 a higher extracellular dopamine output after perfusion of MPP+ than in control MPP+ perfusion expts., in which no DES was administered on day 1. Both Ringer perfusion alone (control Ringer) and coperfusion of 40 nmol DES with 40 nmol MPP+ on day 1 produced on day 2 similar increases in extracellular dopamine output after a second MPP+ perfusion. In the control Ringer experiment, note that the MPP+ on day 2 is the first MPP+ perfusion. Perfusion of 800 fmol FeCl3/15 min along with 40 nmol MPP+ and 400 fmol DES on day 1 completely abolished on day 2 the neuroprotective effect found with 40 nmol MPP+ and 400 fmol DES; 800 fmol FeCl3 did not increase the neurotoxic effect of 40 nmol MPP+ perfusion. The ability of DES to

protect against MPP+ toxicity may indicate a therapeutic strategy in the treatment of diseases when iron is implicated.
OS.CITING REF COUNT: 29 THERE ARE 29 CAPLUS RECORDS THAT CITE THIS RECORD (30 CITINGS)

L9 ANSWER 14 OF 15 CA COPYRIGHT 2010 ACS on STN
ACCESSION NUMBER: 126:153805 CA
ORIGINAL REFERENCE NO.: 126:29646h,29647a
TITLE: Calpain activation and not oxidative damage mediates L-2-chloropropionic acid-induced cerebellar granule cell necrosis
AUTHOR(S): Widdowson, P. S.; Gyte, A.; Upton, R.; Foster, J.; Coutts, C. T.; Wyatt, I.
CORPORATE SOURCE: Neurotoxicology Research Group, Zeneca Central Toxicology Laboratory, Alderley Park, Cheshire, SK10 4TJ, UK
SOURCE: Toxicology and Applied Pharmacology (1997), 142(2), 248-255
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Possible biochem. events involved in L-2-chloropropionic acid (L-CPA)-induced delayed cerebellar granule cell necrosis following N-methyl-D-aspartate activation were studied in vivo. We examined whether the calcium-sensitive proteolytic enzymes, the calpains, may be activated by L-CPA or whether the generation of excess quantities of cytotoxic free radicals may play a role in the neurotoxicity produced by oral administration of L-CPA (750 mg/kg, pH 7.0). Evidence for free radical-induced cellular damage was examined using biochem. approaches such as examining brains from L-CPA-treated rats for increased lipid peroxidn., DNA damage, or protein oxidation Second, the ability of antioxidants to provide neuroprotective activity against L-CPA-induced neurotoxicity was examined in vivo. Western blotting using antibodies against spectrin (α-fodrin) demonstrated evidence for calpain (EC 3.4.22.17) activation in the cerebellum, but not in the cerebral cortex of L-CPA-treated rats at 36 and 48 h after L-CPA dosing. In contrast, there was no evidence for oxidative damage to cerebellar proteins or lipids in L-CPA-treated rat brains compared to controls. We also could not find evidence for DNA damage using the TUNEL method for the detection of single- and/or double-strand breakage in situ in L-CPA-treated brains. We examined whether a number of reported antioxidants may be effective against L-CPA-induced neurotoxicity. The aminosteroids U74389G and U83836E, the free radical scavengers 3-methyl-1-phenylpyrazolin-5-one and N-tert-butylphenylnitrone, and the iron chelator N-ethoxy-2-ethyl-3-hydroxypyridin-4-one were all ineffective in attenuating L-CPA neurotoxicity. We suggest that L-CPA-induced cerebellar necrosis is the result of calpain activation which results in the degradation of cytoskeletal proteins and other proteins necessary for cellular biochem. We could find no evidence of oxidative damage to cerebellar proteins, lipids, or DNA as a result of excess amts. of free radicals, and selective antioxidants were unable to provide neuroprotection against L-CPA neurotoxicity, suggesting that oxidative stress does not play a role in the granule cell necrosis.
AB Possible biochem. events involved in L-2-chloropropionic acid (L-CPA)-induced delayed cerebellar granule cell necrosis following N-methyl-D-aspartate activation were studied in vivo. We examined whether

the calcium-sensitive proteolytic enzymes, the calpains, may be activated by L-CPA or whether the generation of excess quantities of cytotoxic free radicals may play a role in the neurotoxicity produced by oral administration of L-CPA (750 mg/kg, pH 7.0). Evidence for free radical-induced cellular damage was examined using biochem. approaches such as examining brains from L-CPA-treated rats for increased lipid peroxidn., DNA damage, or protein oxidation Second, the ability of antioxidants to provide neuroprotective activity against L-CPA-induced neurotoxicity was examined in vivo. Western blotting using antibodies against spectrin (α-fodrin) demonstrated evidence for calpain (EC 3.4.22.17) activation in the cerebellum, but not in the cerebral cortex of L-CPA-treated rats at 36 and 48 h after L-CPA dosing. In contrast, there was no evidence for oxidative damage to cerebellar proteins or lipids in L-CPA-treated rat brains compared to controls. We also could not find evidence for DNA damage using the TUNEL method for the detection of single- and/or double-strand breakage in situ in L-CPA-treated brains. We examined whether a number of reported antioxidants may be effective against L-CPA-induced neurotoxicity. The aminosteroids U74389G and U83836E, the free radical scavengers 3-methyl-1-phenylpyrazolin-5-one and N-tert-butylphenylnitrone, and the iron chelator N-ethoxy-2-ethyl-3-hydroxypyridin-4-one were all ineffective in attenuating L-CPA neurotoxicity. We suggest that L-CPA-induced cerebellar necrosis is the result of calpain activation which results in the degradation of cytoskeletal proteins and other proteins necessary for cellular biochem. We could find no evidence of oxidative damage to cerebellar proteins, lipids, or DNA as a result of excess amts. of free radicals, and selective antioxidants were unable to provide neuroprotection against L-CPA neurotoxicity, suggesting that oxidative stress does not play a role in the granule cell necrosis.

OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

L9 ANSWER 15 OF 15 CA COPYRIGHT 2010 ACS on STN

ACCESSION NUMBER: 119:63949 CA

ORIGINAL REFERENCE NO.: 119:11337a,11340a

TITLE: Basic FGF, NGF, and IGFs protect hippocampal and cortical neurons against iron-induced degeneration

AUTHOR(S): Zhang, Ying; Tatsuno, Tohru; Carney, John M.; Mattson, Mark P.

CORPORATE SOURCE: Sanders-Brown Res. Cent. Aging, Univ. Kentucky, Lexington, KY, 40536-0230, USA

SOURCE: Journal of Cerebral Blood Flow and Metabolism (1993), 13(3), 378-88
CODEN: JCBMDN; ISSN: 0271-678X

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Iron is believed to contribute to the process of cell damage and death resulting from ischemic and traumatic insults by catalyzing the oxidation of protein and lipids. Exposure of cultured rat hippocampal neurons to iron (FeSO4) caused a dose-dependent reduction in neuronal survival, which was potentiated by ascorbate. Damage to neurons was associated with a significant level of oxygen radical in the culture medium. The iron chelator desferal prevented both the neuronal degeneration caused by FeSO4 and the production of oxygen radical, demonstrating that ionic iron was responsible for the cell damage. Iron neurotoxicity was associated with an elevation of [Ca2+]i and was attenuated by NMDA receptor antagonists. Since recent findings demonstrated

neuroprotective effects of growth factors in cell culture and in vivo models of ischemia, the effects of growth factors on iron-induced damage were studied. Basic fibroblast growth factor (bFGF), nerve growth factor (NGF), and insulin-like growth factors (IGF-I and IGF-II) each protected neurons against iron-induced damage. Both rat hippocampal and human cortical neurons were protected by these growth factors. Taken together, the data suggest that the neuroprotective effects of growth factors against excitotoxic/ischemic insults may result, in part, from a prevention or attenuation of oxidative damage.

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OS.CITING REF COUNT: 113 THERE ARE 113 CAPLUS RECORDS THAT CITE THIS RECORD (113 CITINGS)

=> d his

(FILE 'HOME' ENTERED AT 14:20:56 ON 25 FEB 2010)

FILE 'REGISTRY' ENTERED AT 14:21:10 ON 25 FEB 2010

L1 STRUCTURE UPLOADED
L2 39 S L1 SAM
L3 578 S L1 FULL

FILE 'CA' ENTERED AT 14:21:49 ON 25 FEB 2010

L4 258 S L3
L5 6630 S IRON CHELAT?
L6 20 S L5 AND L4
L7 77 S (IRON CHELATOR) AND NEUROPROTECTIVE
L8 61 S L7 NOT L6
L9 15 S L8 AND PY<2002

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---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

STN INTERNATIONAL LOGOFF AT 14:31:21 ON 25 FEB 2010